Halothane–Epinephrine-induced Cardiac Arrhythmias and the Role of Heart Rate

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The authors previously showed that cyclopropane–epinephrine-induced bigeminal arrhythmias can best be explained by a re-entrant mechanism. They have now obtained evidence for re-entry in bigeminal arrhythmias during infusions of epinephrine (0.5–3 μg/kg/min) in dogs anesthetized with 0.8 per cent halothane. Both a critical level of blood pressure and a critical increase in heart rate were necessary for arrhythmias to be induced in any given animal. Artificial elevation of the blood pressure during infusion of a subthreshold dose of epinephrine could induce bigeminy, and the arrhythmia could be aborted by a sudden reduction of blood pressure. The heart rate accelerated approximately 40 beats/min prior to the onset of bigeminy, and atrial pacing at similarly increased rates during a subthreshold infusion of epinephrine could induce bigeminy. Stimulation of the peripheral end of the cut right cervical vagus reduced heart rate and converted bigeminy to sinus rhythm. Bradycardia was not the sole mechanism of the vagal effect since conversion to sinus rhythm could also be achieved with more rapid stimulation of the vagus when the heart rate was maintained constant by atrial pacing. Under these conditions further acceleration of the heart rate could reinduce a bigeminal arrhythmia that was again sensitive to further increases in the frequency of vagal stimulation, and it is concluded that the vagus acts on the spread of the re-entrant impulse. This is best shown with cyclopropane anesthesia, because AV-nodal block occurs more easily with halothane. In addition, very brief periods of increased heart rate caused prolonged periods of bigeminy, which indicates that changes in heart rate may alter the electrophysiology of the halothane-sensitized myocardium to promote bigeminal arrhythmias by a re-entry mechanism. (Key words: Heart, arrhythmia; Anesthetics, volatile, halothane.)

Since the early studies of Ravnitos,¹ it has been recognized that halothane resembles other hydrocarbons in its ability to sensitize the heart to the arrhythmogenic effects of epinephrine. Although in-vitro evidence indicates that this anesthetic depresses ventricular automaticity,²,³ in-vivo experiments by Hashimoto and Hashimoto⁴ suggest that the sensitizing action of halothane is due primarily to slowing of the heart rate by halothane, which in turn allows emergence of a ventricular pacemaker in response to epinephrine. Their suggestion reopened the discussion concerning the mechanism of hydrocarbon–epinephrine-induced arrhythmias, in that it stands in opposition to the evidence from this laboratory that these arrhythmias are due to a re-entry phenomenon.⁵–⁷ Our conclusions, based on studies with cyclopropane in-vivo, are supported to some extent by the studies with both cyclopropane and halothane in isolated tissues, where in addition to depression of automaticity, changes in conduction velocity, in refractory period and in duration of action potential have been reported.⁸,⁹ These are consistent with the combination of slowed conduction and unidirectional block now generally accepted to be necessary for re-entry to occur.

Subsequent to the completion of the present study, Hashimoto et al. described experiments that led them to revise their conclusions and to support re-entry as the mechanism of these arrhythmias.⁵ There remains, however, a key issue which has not been dealt with adequately. This is the role of heart rate in the induction of ventricular arrhythmias. Although it is obvious that a slow atrial rate will predispose to the appearance of a ventricular pacemaker, it is also known that changes in heart rate affect re-entry.¹⁰,¹¹

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The present study was designed to investigate the characteristics of bigeminy produced by epinephrine during anesthesia with halothane and to compare the features of these arrhythmias with those that occur under identical conditions with cyclopropane anesthesia. In addition, detailed consideration was given to the role of heart rate in the generation of these arrhythmias.

Methods

Experiments were performed on 24 mongrel dogs of either sex weighing 10–16 kg. Anesthesia was induced with sodium thiopental (20 mg/kg, iv), and a tracheal cannula was inserted for mechanical ventilation at a frequency of 18/min with a tidal volume of 20–25 ml/kg. Anesthesia was mainained in five animals with 20 per cent cyclopropane as described previously or with 0.8 per cent halothane in oxygen delivered in a nonrebreathing system through a Fogerger Copper Kettle vaporizer. The use of a Beckman Medical Gas Analyzer (Model LB-1) in studies of three dogs showed that inspiratory and expiratory anesthetic concentrations equilibrated within 17–20 minutes. During this interval no recordings were taken, but bilateral vagotomy was performed and the left carotid artery was cannulated for measurement of arterial blood pressure with a Statham P23-A transducer. The chest was entered either through the midline or through the right fourth intercostal space and the pericardium was incised. Two pairs of platinum electrodes were sewn to the right atrium to permit pacing and to record the atrial electrogram. A lead II electrocardiogram was recorded from the periphery. In some animals a soft ligature was placed around the thoracic aorta to allow manipulation of the blood pressure by partial compression.

Tektronix stimulators with isolation transformers were used to pace the right atrium (twice threshold voltage: 5 msec pulse duration) and to stimulate the peripheral end of the cut right vagus nerve (1–20 Hz). Epinephrine bitartrate (doses expressed as the free base) was infused by a Harvard pump into a femoral vein. A minimum of 15 minutes was allowed for recovery following each infusion. All variables were recorded on a Grass model P-5 polygraph. Experiments were terminated within 3 hours of the first exposure to the anesthetic.

Results

Characteristics of Thiopental–Halothane–Epinephrine–Induced Arrhythmias

Bigeminal arrhythmias were repeatedly produced in all animals anesthetized with halothane by intravenous infusions of epinephrine (0.5–3.0 μg/kg/min). The rate of epinephrine infusion necessary for bigeminy to occur remained relatively constant throughout the period of recording. Bigeminy was induced a minimum of four times in each experiment. The mean dose of epinephrine effective in producing bigeminy was 1.3 ± 0.1 μg/kg/min in 19 animals. More rapid rates of infusion led to the development of multifocal ventricular arrhythmias. Ventricular fibrillation did not occur at the doses tested.

The bigeminal electrocardiogram (EKG) recorded in the present study with halothane showed the characteristic features of bigeminy previously found with cyclopropane. The coupling interval (Q-Q) was constant or varied within very narrow limits (10–15 msec). The QRS complexes of the bigeminal beats were prolonged in duration, although their polarity was only rarely inverted. The P-R interval of the bigeminal beat was invariably shorter than that of the preceding normal beat, and in many cases the configuration of the bigeminal QRS complex obscured the P-wave entirely or in part. Nevertheless, inspection of the atrial electrogram showed that the P-P interval remained constant.

Role of the Blood Pressure

Previous experiments with animals anesthetized with cyclopropane had shown that the arterial blood pressure is a critical factor influencing the development of both bigeminal and multifocal arrhythmias. This was also found to be true of halothane. Independent of variations in the rate of infusion of epinephrine, bigeminy occurred...
only when a critical level of blood pressure was reached. This level was constant in any given dog but varied among animals. The coefficient of variation of the systolic arterial pressure at the onset of bigeminal arrhythmia did not exceed 6 per cent in any dog. In 19 animals, the systolic and diastolic blood pressures at the onset of arrhythmia were 161 \pm 6 and 132 \pm 5 mm Hg, compared with control values of 104 \pm 3 and 84 \pm 3 mm Hg. The onset of bigeminy was in virtually all cases accompanied by a complete pulse deficit, such that systolic pressure was considerably increased whereas diastolic pressure was decreased.

As shown in figure 1A, bigeminal arrhythmias could be initiated by aortic compression during infusion of a subthreshold dose of epinephrine. This maneuver artificially elevated the thoracic arterial pressure to levels comparable to those occurring after effective doses of epinephrine without altering the intrinsic cardiac rate. In each case the arrhythmia subsided within 10 seconds after the release of aortic compression. The induction of arrhythmias in this manner was demonstrated on 19 occasions in eight of nine animals. On four occasions the identical maneuver was performed in the absence of epinephrine infusion and arrhythmias did not occur.

The importance of blood pressure elevation to the development of bigeminy was further demonstrated by the effects of hypotension during ongoing bigeminal arrhythmias. In four dogs the arterial pressure was fixed to an artificially high level by compression of the thoracic aorta and arrhythmias were produced by the necessary infusions of epinephrine. Subsequently, the aortic compression was released, and in each case a normal sinus rhythm was restored (fig. 1B).

**EFFECTS OF ATRIAL RATE**

In addition to the necessary elevation of arterial pressure, the ability of epinephrine to induce bigeminy was dependent upon the attainment of a critical cardiac rate. For any given dog the heart rate at the onset of bigeminy was remarkably constant, and in no case did the coefficient of variation exceed 4 per cent. An increase of approximately 40 beats/min was necessary for the induction of bigeminy with an epinephrine infusion.

**Fig. 1.** Influence of arterial blood pressure on cardiac arrhythmias during halothane anesthesia. **A**, induction of bigeminal arrhythmia by compression of the thoracic aorta during a subthreshold (1 \( \mu g/kg/min \)) infusion of epinephrine. **B**, conversion of bigeminy to sinus rhythm by hypotension produced by the withdrawal of aortic compression during a 2 \( \mu g/kg/min \) infusion of epinephrine. **Upper traces:** lead II electrocardiogram. **Middle traces:** atrial electrogram (atrial potentials marked "P"). **Lower traces:** carotid arterial blood pressure.
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FIG. 2. Influence of heart rate on bigeminal arrhythmias during halothane anesthesia. A, induction of bigeminy by atrial pacing at a rate of 150 beats/min (sinus rate, 130 beats/min) during a sub-threshold (0.5 μg/kg/min) infusion of epinephrine. B, conversion of bigeminy to sinus rhythm by acceleration of the atrial pacing rate from 188 to 240 beats/min. C, maintenance of bigeminal arrhythmia with a constant coupling interval despite acceleration of the atrial pacing rate from 150 to 188 beats/min. Epinephrine infusion is 1 μg/kg/min. (Abbreviations as in fig. 1.)

the first instance of bigeminy occurring in each of the 19 animals studied, the mean heart rate was 167 ± 4 beats/min, as opposed to a mean control rate of 126 ± 3 beats/min.

The contribution of an increased heart rate to the development of bigeminy could also be shown by the effects of atrial pacing during infusions of subthreshold doses of epinephrine. Artificially induced increases in atrial rate induced bigeminal arrhythmias regularly in eight of 11 dogs (fig. 2A). However, it was occasionally shown that the bigeminy induced by this cardioacceleration continued for as long as 60 seconds after the cessation of atrial pacing. This “conditioning” was further demonstrated by limiting the period of atrial pacing to a brief train of 5–15 impulses. Under these conditions, bigeminy was occasionally triggered during the last few paced beats and continued for as long as 90 seconds (four dogs). Arrhythmias occurred during subthreshold epinephrine infusions only when the cardiac rate was initially increased to a level similar to or in excess of that produced by effective doses of epinephrine.

As shown in figure 2B, it was also possible to restore sinus rhythm during bigeminy by overly rapid pacing of the atrium. This effect was demonstrated in seven dogs either when the atrial rate was increased further during infusion of subthreshold doses of epinephrine or when the atria were paced rapidly during arrhythmias induced by adequate doses of epinephrine. In most cases the “overdrive” rate to stop bigeminal rhythm was constant in a given animal.

Within the relatively wide range of heart rates found to be compatible with sustained bigeminal arrhythmias, changes in the atrial pacing rate did not alter the coupling interval or the configuration of the bigeminal EKG (fig. 2C).

EFFECT OF STIMULATION OF THE VAGUS AND THE ROLE OF ATRIAL RATE

Stimulation of the right cervical vagus nerve restored sinus rhythm during bigeminy. Stimulation of the left vagus was effective less regularly. Figure 3A shows that conversion was coincident with a reduction of the atrial rate. This could be interpreted to be
due to slowing to a rate below the critical rate necessary to sustain bigeminy. Although bradycardia was usually observed, this could not be the sole mechanism of conversion to sinus rhythm. In a few instances arrhythmias were converted to normal sinus rhythm when there was no measurable reduction of the intrinsic atrial rate. Furthermore, we confirmed our previous observation that high-frequency stimulation of the vagus could convert bigeminy to a sinus rhythm while the cardiac rate was kept constant by atrial pacing (fig. 3B). This was shown on ten of 12 occasions in five dogs. The bigeminal arrhythmias returned within 1 minute (often 20–30 sec) after discontinuation of vagal stimulation.

When stimulation of the vagus had converted the arrhythmia to normal sinus rhythm either at constant atrial rate or accompanied by slowing of the atria, increases in atrial rate caused reappearance of the arrhythmia. This is best shown in animals anesthetized with cyclopropane. Figure 4 shows the results from one of five such experiments. The top row of panels shows that stimulation of the vagus caused conversion of the arrhythmia and slowing of the atrial rate and that arrhythmia returned when the atrial rate was increased to that obtaining prior to conversion. An increase in the frequency of vagal stimulation again converted the arrhythmia (bottom left). Atrial rate and vagal stimulation could now be “titrated” to obtain either bigeminy or normal rhythm. The same type of response could be observed in halothane-anesthetized dogs, but over a smaller range of heart rates because block of AV-nodal conduction interfered.

**Discussion**

Infusion of minimal doses of epinephrine into dogs anesthetized with 0.8 per cent halothane causes constantly-coupled bigeminal arrhythmia. Somewhat higher rates of infusion cause multifocal ventricular arrhythmias. The properties of the bigeminal rhythm under these conditions are virtually identical to those described in detail for cyclopropane–epinephrine-induced arrhythmias. The coupling interval of the arrhythmia is not changed when the heart rate is changed within wide limits, stimulation of the vagus nerve converts arrhythmia to

![Figure 3](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931524/)

Fig. 3. Influence of vagal stimulation on bigeminal arrhythmias during halothane anesthesia. A, conversion of bigeminy to sinus rhythm during .5 μg/kg/min infusion of epinephrine. Stimulation of the vagus nerve at 5 Hz at signal is accompanied by slowing of the sinus rate from 190 to 125 beats/min. B, conversion of bigeminy to sinus rhythm by vagal stimulation (signal) with atrial pacing at a constant rate of 188 beats/min. Epinephrine infusion is 2 μg/kg/min. (Abbreviations as in fig. 1.)
normal sinus rhythm, and occurrence of arrhythmia is critically dependent on an adequate pressor response.

The interrelationship of blood pressure and epinephrine-induced arrhythmias has been found previously in animals anesthetized with a variety of halogenated agents.\(^5\,6\,13\) The blood pressure determines not only the induction of arrhythmia,\(^5\) but also its severity.\(^6\) The reasons for this are not fully understood. It has been observed by several investigators that establishment of the constantly-coupled bigeminy is preceded by a series of three or four beats of variable coupling. Reynolds and co-workers (personal communication) have observed recently that the coupling intervals of these beats are closely correlated with the intraventricular systolic pressure and suggested that stretch may determine coupling. Stretch of Purkinje fibers has been shown to slow conduction velocity and to increase the rate of diastolic depolarization,\(^11\) both of which would encourage re-entry.

The present results add to our observations with cyclopropane in two significant ways. First, we have demonstrated that bringing arterial pressure to threshold levels during subeffective infusions of epinephrine causes bigeminy to appear. This differs from previous work, which imposed changes in blood pres-
sure only during infusions of effective doses of epinephrine.\textsuperscript{5,6} Second, we have now observed that there is a critical atrial rate for the appearance of the arrhythmia, and that atrial pacing can induce arrhythmia during infusion of subeffective doses of epinephrine. This observation is especially important in connection with the differing interpretations of the role of atrial rate in the induction of arrhythmias, and of the importance of atrial slowing in the ability of vagal stimulation to convert bigeminal rhythm to normal sinus rhythm.

Earlier work\textsuperscript{7-14} led us to the conclusion that the bigeminal beat was a fusion beat of a re-entrant impulse originating in the upper portion of the interventricular septum with the next normal beat conducted through the atrioventricular node. This concept is supported by the demonstration in vitro by Reynolds and Chize\textsuperscript{15} that epinephrine potentiates the modest slowing of conduction produced by halothane, and so contributes to a critical factor for re-entry. Hashimoto and Hashimoto\textsuperscript{4} have recently suggested that the mechanism by which halothane sensitizes the heart to arrhythmias is a decrease of the sinus rate and of the maximal sinus rate after epinephrine, which allows the emergence of a ventricular pacemaker of increased automaticity. We found it difficult to agree with this interpretation, and support their recent conclusions confirming re-entry.\textsuperscript{9} Our demonstration that atrial tachycardia causes arrhythmia when subthreshold doses of epinephrine are infused supports a re-entry mechanism, for it is well known that automaticity is subject to "overdrive suppression."\textsuperscript{16} In addition, there is some controversy concerning the effect of halothane on heart rate.\textsuperscript{17} Bradycardia was not regularly observed in the present study, and Joas and Stevens\textsuperscript{18} have reported that halothane does not reduce the cardiac rate in vivo when the threshold dose for arrhythmia due to epinephrine is decreased sixfold. Several studies indicate that halothane actually depresses ventricular automaticity. Logic and Morrow\textsuperscript{19} reported that halothane anesthesia in vivo consistently depressed the ventricular escape time and idioventricular escape rate during supramaximal stimulation of the right vagus nerve. \textit{In vitro} studies support the observation that ventricular automaticity is depressed.\textsuperscript{20} Halothane has been claimed to counteract the effects of epinephrine to increase the slope of phase 4 depolarization,\textsuperscript{2} but this is subject to controversy.\textsuperscript{9}

Although the effects of heart rate obviously occupy a critical role in the induction and maintenance of bigeminal arrhythmias, it would be premature to assume that this influence is mediated only by the frequency of the supraventricular input. Thus, the present study shows that the effects of increased atrial rates may outlast the actual period of stimulation. Bigeminy induced by atrial pacing during subthreshold epinephrine infusions often continued for many seconds after pacing was terminated, and a short burst of rapid atrial beats sometimes induced bigeminal rhythm that continued for 60-90 seconds at a slower heart rate. This indicates that there is a "conditioning effect" of atrial input that acts in a direction opposite to the "overdrive suppression" of pacemaker tissues; we suppose that it acts by maintaining the conditions for re-entry.

The importance of the cardiac rate in the development of bigeminy is further elucidated by the interrelationship of heart rate and vagal stimulation. The original demonstration from this laboratory that stimulation of the vagus nerves converted bigeminy to normal sinus rhythm\textsuperscript{8} indicated that successful conversion of bigeminy still occurred when atrial rate was maintained constant. However, higher frequencies than those required when the sinus node was allowed to slow were necessary. This observation has now been confirmed during halothane anesthesia (fig. 3B). Vick\textsuperscript{19} confirmed conversion of arrhythmia by stimulation of the vagus nerves during chloroform anesthesia, but showed that arrhythmia could be reinduced by speeding the atria during continued stimulation of the vagus. He concluded that slowing of the atria was important, and indeed causal, to the conversion of bigeminy to normal sinus rhythm by the vagus. He pointed out that a ventricular pacemaker site could not be ruled out, although he agreed that a re-entry mechanism appeared more probable. We have now demonstrated (fig. 4) that the arrhythmogenic
effects of increasing the heart rate may be titrated against the rate of vagal stimulation. In this way bigeminy can be alternately induced and converted to a sinus rhythm as these two factors compete, vagal effects tending to restore a sinus rhythm and rate effects tending to reinstate bigeminy. It is probable, therefore, that the vagus influences directly the spread of the re-entrant impulse.

References
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