The phenomenon of "sensitization" of the heart to sympathomimetic amines by hydrocarbon anesthetics has been the subject of numerous investigations. Early studies concerned mainly the development of ventricular fibrillation as a result of sensitization of the heart by chloroform. More recently, interest has centered around the less severe cardiac arrhythmias resulting from small doses of sympathomimetic amines in the presence of cyclopropane. The characteristic arrhythmias observed under these conditions are coupled bigeminal rhythms and monofocal tachycardias.\textsuperscript{1,2} Dresel suggested, on the basis of indirect evidence, that both the bigeminal coupled rhythms and monofocal tachycardias result from re-entry and that they "originate in the A-V node or the bundle of His."\textsuperscript{3} With the use of microelectrode recordings and the recent methods developed by Hoffman and co-workers for recording from different regions of the specialized conduction system in situ,\textsuperscript{4} it has been possible to obtain more direct evidence concerning the origin of these arrhythmias. In the present studies monofocal tachycardia and bigeminal coupled rhythms always originated distal to the bundle of His electrode.

Methods

IN SITU STUDIES

Mongrel dogs weighing 25 to 35 kg were anesthetized with thiopental sodium (20 mg/kg) given intravenously. The trachea was intubated; artificial respiration was provided with oxygen from an intermittent positive pressure respirator. A femoral artery and vein were cannulated. A right thoracotomy was performed in the fourth intercostal space, the azygos vein was ligated, and occluding tapes were placed around the cranial and caudal vena cavae. The pericardium was opened and a right atriotomy performed. During venous inflow occlusion an electrode was placed over the bundle of His and sutured in place. The atriotomy was closed with a continuous suture and additional electrodes were sutured to the epicardial surface of both ventricles and the right atrium. The vagi were exposed in the neck.

Lead II of the electrocardiogram was recorded together with bipolar electrograms from the right atrial appendage, bundle of His, and left and right ventricles on an Electronics for Medicine recorder. The vagi were cooled when desired by notched silver bars whose distal ends were immersed in iced brine. Peripheral vagal stimulation was carried out using a Grass C-4 stimulator after crushing or cooling the nerve. Cyclopropane anesthesia (20% v/v) was administered in a closed circle absorption system; the respirations were manually controlled. One-half hour after the beginning of cyclopropane administration, norepinephrine or epinephrine was injected intravenously in a volume of 5 ml over a period of one minute. The doses used ranged from 1 to 10 µg/kg. Injections were repeated at intervals of ten minutes or longer.

STUDIES ON ISOLATED TISSUES

A preparation consisting of the anterior papillary muscle, right ventricular wall, and free-running false tendons was isolated from the right ventricles of dogs anesthetized with pentobarbital (25 mg/kg). The tissue was bathed with Tyrode's solution in a 40-ml muscle bath and gassed with 5% carbon dioxide in oxygen. Temperature was maintained at 37°C. Spontaneous activity was recorded with glass capillary microelectrodes having a tip diameter of less than 0.5 micron. The microelectrodes were filled with 3 M KCl and had a resistance of 10 to 50 megohms. Transmembrane potentials of Purkinje and an-
terior papillary muscle fibers were recorded simultaneously using cathode followers, d-c amplifiers, and a dual beam oscilloscope. Epinephrine was added directly to the muscle chamber. Unexpectedly large amounts were required to initiate arrhythmias, possibly because of oxidation of the amine in the presence of high oxygen tension, high pH, and the trace amounts of heavy metals which were present in the reagents used to make up the Tyrode’s solution.

Results

COUPLED RHYTHMS

Coupled rhythms were observed repeatedly during cyclopropane anesthesia in five of the six animals studied. They were produced by doses of norepinephrine ranging from 2 to 6 μg/kg. Sixteen satisfactory tracings comprise the data presented here. In these records the His electrogram of the abnormal beat was either 1) present with normal configuration, 2) inverted, or 3) not distinguishable.

An example of the first type is shown in figure 1. Electrograms were recorded from the right atrium, bundle of His, and right ventricle together with the lead II electrocardiogram during a bigeminal and coupled rhythm induced by norepinephrine (2 μg/kg). Activity at the atrium (a), bundle of His (h), and right ventricular septum (s) is recorded in the bundle of His electrogram. The atrial-His interval (a-h) and the His bundle complexes are identical in both normal and coupled beats. During the normal beat depolarization of the His bundle occurs before the QRS complex in lead II; however, during the abnormal beat the His bundle complex follows the onset of the R wave. The constant His bundle to right ventricle conduction interval and unvarying configuration of the right ventricular electrogram suggest that this ventricle was normally activated. However, the coupled beats have an abnormally short His-septal interval (h-s), indicating that depolarization of the septum could not have resulted from activation of the bundle of His. The fact that ventricular depolarization (lead II) precedes the His complex (h) means that some part of the ventricular myocardium (presumably the left) was activated by an abnormal mechanism not involving the bundle of His.

Retrograde activation of the bundle of His is illustrated in figure 2. During the normal beat the His bundle deflection (h) is initially negative, then positive. This sequence is reversed in the coupled beat, and the inscription of the His bundle deflection is preceded by a ventricular depolarization signal in both the right ventricular electrogram and the lead II electrocardiogram. These observations rule out the possibility that the coupled beat was ac-
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FIGURE 3
Symbols and time lines as in figure 1. A bigeminal coupled rhythm is shown in which activation of the bundle of His cannot be observed during the coupled beat.

In figure 3 the His bundle potential of the coupled beat is not visible, but ventricular depolarization precedes any electrical activity in the His bundle recording. Possible explanations for this finding include: 1) simultaneous activation of the His bundle and septum, 2) refractoriness of the bundle, and 3) asynchronous activation of the bundle, resulting in a low amplitude, attenuated electrogram which was not recorded. The last two possibilities are considered unlikely. No matter which of these explanations is correct, the ventricle could not have been activated normally via the His bundle.

In figure 4 a coupled bigeminal rhythm is illustrated in which the "normal" beat originates in the A-V node or upper His bundle. In the top tracing are shown electrograms from the right atrium and ventricle. The first complex on the left is typical of an A-V nodal beat, with the His bundle complex (h) preceding ventricular and atrial depolarization. The right ventricular complex precedes the left by 19 msec. In the coupled beat the left ventricular depolarization signal occurs 11 msec before that from the right ventricle. The His bundle electrogram (h) is atypical and may in part represent septal activation. The fact that no electrical activity was recorded prior to ventricular depolarization (lead II) means that the ventricles were not activated normally via the His bundle.

The conclusion that activation of the ventricles during coupled rhythms can occur from sites below the bundle of His is further supported by studies on isolated tissues. In figure 5A are shown transmembrane action potentials from a Purkinje fiber (above) and a ventricular papillary muscle fiber (below) bathed with Tyrode's solution containing epinephrine (0.7 µg/ml). A spontaneous coupled rhythm is present, with two normal beats (n) preceding each coupled (c) response. Using a more rapid sweep velocity it was observed that Purkinje activation preceded ventricular activation. This indicates that coupled beats can originate in the absence of the A-V node, the bundle of His, and the bundle branches.

VENTRICULAR TACHYCARDIA

Monofocal ventricular tachycardia was observed repeatedly in every animal studied. These rhythms were produced by doses of norepinephrine ranging from 4 to 8 µg/kg during cyclopropane administration. Following larger doses multifocal ventricular tachycardias were observed. In figure 6 a typical example of monofocal tachycardia is shown. At the left is a normal tracing; to the right is shown ventricular tachycardia. During the ventricular rhythm the His bundle complex

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appears following ventricular depolarization and is opposite in polarity to that of the normal complex. Excitation of the ventricles therefore depends upon activity originating below the His bundle electrode. The interval between succeeding right ventricular deflections is constant and is shorter than that separating right atrial deflections. Therefore there are at least two pacemakers, a rapid one driving the ventricles and a slower one activating the atria.

Intracellular recordings from the Purkinje system and attached ventricular muscle indicate that increased automaticity resulting from epinephrine can cause monofocal ventricular tachycardia. Following the addition of 2.0 \( \mu g \) of epinephrine per ml of Tyrode’s solution, the rate of spontaneous activity in the Purkinje fibers increased, and diastolic depolarization was conspicuous (fig. 5B). It could be demonstrated that activation of the Purkinje fiber preceded ventricular depolarization, indicating that the Purkinje fiber was driving the ventricular muscle under these conditions. Diastolic depolarization was never observed in ventricular muscle fibers.

**EFFECTS OF VAGAL STIMULATION**

Vagal stimulation during normal sinus rhythm increased the interval between atrial and His bundle activation, and this maneuver was employed routinely to verify placement of the His bundle electrode. During coupled ventricular rhythms induced by norepinephrine, varying degrees and frequencies of vagal stimulation failed to convert the arrhythmia to normal sinus rhythm in two of three animals, and did not consistently increase the coupling interval in any animal. In the dog whose rhythm was converted to normal by vagal stimulation, the conversion was always preceded by bradycardia and a conspicuous decrease in mean arterial blood pressure. Vagal stimulation during monofocal tachycardia failed to convert the tachycardia either to bigeminal or to normal rhythm, but it did cause the rhythm to become irregular and the ventricular complexes (lead n) to vary in configuration from one beat to another.

**Discussion**

Dresel has suggested that coupled rhythms observed during cyclopropane anesthesia following the injection of small doses of a catecholamine are caused by re-entry in the A-V node or upper His bundle. The evidence for this was indirect. Briefly, he observed that the coupling interval remained constant even when the rate of atrial contraction was increased by electrical pacing. Also, vagal stimulation increased the coupling interval, and in most cases caused reversion to sinus rhythm.

Our evidence, derived from simultaneous electrograms from the right atrium, right and left ventricles, and bundle of His, indicates that the ventricles were not normally activated during the coupled beat and that activity was originating from below the His bundle elec-
trode. Although an abnormal QRS complex can result from supraventricular activation traversing the A-V node and His bundle if part of the conducting system is refractory, the fact that ventricular depolarization preceded the His electrogram shows clearly that this did not occur in any of the animals studied. Usually the abnormal activity originated in the left ventricle distal to the His bundle. The evidence for this is that: 1) septal activation usually occurred before right ventricular depolarization (fig. 1); 2) when bilateral ventricular electrograms were obtained, left ventricular activation usually preceded that on the right (fig. 4); and 3) most frequently in lead II an initial R wave appeared during the coupled beat. The results of the in vivo studies do not permit further definition of either the site of activation or the mechanism involved. Evidence obtained in vitro suggests that coupled rhythms may result from premature depolarization of peripheral Purkinje fibers (fig. 5A).

Dresel suggested that monofocal tachycardias also originated from re-entry in the A-V node or upper bundle of His, since vagal stimulation converted the tachycardia either to a coupled or a sinus rhythm. In our animals, the predominant pacemaker during monofocal tachycardia was in the ventricles and the His bundle was activated antidromically. Vagal stimulation did not convert this arrhythmia either to a coupled rhythm or to sinus rhythm; instead, the rhythm became irregular and the ventricular complexes varied in configuration from one beat to another. These results are inconsistent with Dresel's hypothesis, and suggest instead increased automaticity in the ventricular specialized conducting system. This view is supported by observations in isolated tissue showing rapid diastolic depolarization in Purkinje fibers in the presence of epinephrine (fig. 5B).

We do not know the reason for the discrepancy between our results and Dresel's during vagal stimulation. Several possibilities exist: 1) the pacemaker in Dresel's studies may have been in the A-V node or upper bundle of His and consequently subject to vagal suppression; 2) the change in rhythm may have been a result of slowing of the sinus rate or a decline in blood pressure or both; 3) a different intensity of vagal stimulation may have been employed and both parasympathetic and sympathetic efferent fibers coursing in the vagus may have been activated; 4) thoracotomy, atriotomy, and placement of electrodes on the His bundle may have modified the response; or 5) the arrhythmia seen by Dresel may have been atrial in origin. Although the last possibility is unlikely, we have seen what appeared to be a monofocal ventricular tachycardia on the electrocardiogram which was determined from the bundle of His electrogram to be aberrant ventricular conduction resulting from rapid atrial pacemaker activity.

It should be emphasized that coupled rhythms and ventricular tachycardias can be readily produced in the absence of cyclopropane. We frequently observed coupled rhythms following the release of inflow occlusion in the presence only of thiopental anesthesia. Similarly, autonomic innervation of the heart is unnecessary, since coupled rhythms can occur in the heart-lung preparation. These rhythms are pressure-sensitive; however, even increased intraluminal pressure is unnecessary, since coupled rhythms can be observed in an isolated Purkinje fiber-papillary muscle preparation (fig. 5). These results suggest that coupled rhythms occur in such varied circumstances that it may be dangerous to assume that a common mechanism is operating. Although re-entry has been most commonly suggested as the mechanism of coupling, direct evidence is nonexistent.

Summary

1. Electrograms have been recorded simultaneously from the right atrium, bundle of His, and both ventricles, together with the lead II electrocardiogram in dogs receiving cyclopropane and oxygen. Following the administration of norepinephrine, both bigeminal rhythms and monofocal ventricular tachycardias were observed.

2. In our studies both the coupled and the monofocal ventricular beats originated distal to the His electrode.

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3. The mechanism of the coupled beats could not be analyzed using either gross or intracellular recording methods; the monofocal tachycardias appeared to result from increased pacemaker activity in the ventricular conducting system.

4. The present results emphasize the hazards of proposing mechanisms to explain arrhythmias solely on the basis of electrocardiographic evidence.

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References


ERRATUM

In the June 1964 issue (volume XIV, no. 6, page 519) graphs above the words Figure 3 and Figure 4 are transposed. The graph, headed EXP. 1-11-63, EPINEPHRINE, placed by mistake at top of page, left, should have appeared at lower right of same page, over the designation Figure 4 and legend. Conversely the graph headed EXP. 1-16-63(B), L. STELL. STIM., placed by mistake at lower right of page 519, should have appeared at upper left of same page over the designation Figure 3 and legend. In summary the figure numbers and legends were correctly placed but the graphs were transposed.
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