The phenomenon of vagal escape refers to two responses of the heart to enhanced efferent vagal nerve activity. First, when cardiac slowing is produced by vagal stimulation, there is generally a gradual return of heart rate toward control levels. In addition, when cardiac asystole is produced by vagal stimulation, rhythmic pacemaker activity usually develops in some area of the specialized conduction system other than the sinoatrial node. In some early studies of vagal escape, only aortic and venous pressures were recorded to indicate heart activity; these measurements did not permit localization of pacemaker sites. Several investigators have suggested, after careful analysis of the electrocardiogram, that during vagal escape pacemaker activity can develop in the atrium, A-V node, or ventricles.

Techniques have been developed recently which make it possible to record surface potentials directly from the specialized conduction system of the intact heart. The purpose of this study was to employ these techniques to define more clearly the nature of escape rhythms and to obtain data regarding the influence of isoproterenol on the location and rate of pacemaker sites during vagal escape.

**Methods**

Experiments were performed on mongrel dogs of both sexes, weighing 16 to 22 kg. Anesthesia was induced with pentobarbital sodium (25 mg/kg iv). Ventilation was controlled with a Jefferson pump and body temperature was maintained with external heating pads.

A right thoracotomy was performed through the fourth intercostal space and the pericardium was opened and used to cradle the heart. During inflow occlusion, the right atrium was opened and

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a bipolar recording electrode was implanted over the bundle of His. The atrium was then allowed to fill and was closed with sutures. The duration of inflow occlusion averaged two minutes. A second bipolar electrode was sutured to the epicardial surface of the right atrium in the region of the sinoatrial node (fig. 1). Signals from each electrode were amplified with Tektronix 122 preamplifiers. The outputs were displayed on a Tektronix 502 dual beam oscilloscope and photographed with a Dumont 321 camera at a paper speed of 400 inches per minute. Frequencies below 80 cycles/sec and above 1000 cycles/sec were filtered out to sharpen the desired signals.

Aortic and right atrial pressures were recorded through catheters introduced down the left carotid artery and the right external jugular vein respectively. Pressures were measured by Statham transducers and recorded on a Sanborn multi-channel direct-writing oscillograph.

Either the right or left vagus nerve (occasionally both) was isolated in the neck and crushed or severed proximally. The distal end of the vagus was placed in a stimulating electrode and bathed in mineral oil. Temperature in the neck was maintained by a heated collar. The nerve was stimulated through an isolation unit, using a Grass impulse generator. Stimulation variables were adjusted to produce maximal cardiac slowing; usual values were 8 to 10 volt pulses of 5 msec duration at a frequency of 20 to 30 per second. When maximal and reproducible cardiac responses to vagal stimulation had been established the stimulation variables were then held constant.

The following protocol was observed in each experiment. The response to approximately 30 seconds of vagal stimulation was determined by simultaneous recordings of aortic and right atrial pressures as well as electrograms from the region of the SA node and His bundle. Isoproterenol (2 or 4 \( \mu \)g/cc) was then infused at selected rates (1.8 \( \mu \)g/min to 10.2 \( \mu \)g/min) into the right femoral vein. After three to five minutes of infusion the response to vagal stimulation was redetermined. Isoproterenol infusion was then discontinued and five to eight minutes later the response to vagal stimulation was examined a third time. Only those experiments in which the responses to vagal stimulation were essentially identical during the control periods before and after the infusion were considered for analysis of isoproterenol effects.

**Results**

**PACEMAKER ACTIVITY DURING VAGAL ESCAPE**

Vagal stimulation produced an initial period of ventricular asystole in seven of eight ani-

![FIGURE 2](https://example.com/figure2.png)

**FIGURE 2**


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VAGAL ESCAPE

A.
CONTROL

SA

A

H

S

B.
VAGUS

VE #5

SA

H

A

S

C.

VE #8

SA

A

H

S

D.

500 m sec

FIGURE 3


mals. Following variable periods of cardiac arrest a regular escape rhythm was established in the majority of experiments. The electrograms indicated local depolarization of the SA node (SA), interatrial septum (A), bundle of His (H), and basal interventricular septum (S). The anatomic level of the pacemaker could be classified as above the A-V node, in the region of the A-V node, or below the A-V node from analysis of the sequence of activation at these positions. During vagal escape rhythmic pacemaker activity was observed at each level.

Figure 2 (upper) shows records from an experiment in which the vagal escape mechanism was above the A-V node. During both the control period (A) and during vagal stimulation (B) atrial activity preceded His complex, the His complex was of constant polarity and contour, and the H-S interval was constant. The pacemaker remained in the region of the sinoatrial node since the SA complex was essentially unaltered by vagal stimulation and preceded activity from the interatrial septum by a constant interval. Vagal influence on the A-V node was reflected by the lengthened A-H interval in panel B. In figure 2 (middle) records are presented from an experiment in which the escape mechanism was supranodal with 2:1 A-V block. Panel C shows the control records prior to vagal stimulation. In D, during vagal stimulation, alternate atrial beats failed to propagate through the A-V node.

Stimulation of the vagus nerve produced asystole or marked slowing of the atrium in all animals studied. In those experiments in which atrial asystole was produced, no electrical activity was recorded from the SA node or the atrial septum. Atrial slowing was associated with sinus bradycardia, (fig. 2, upper), or with a shift in location of the atrial pacemaker. Figure 2 (lower) shows an example of the latter; the atrial complexes were changed and there was an alteration of the interval between SA node and atrial septum.

Figure 3 (upper) shows records from an experiment in which the vagal escape rhythm originated in the region of the A-V node. During the control period (A) the SA node and interatrial septum preceded His and the His complex was diphasic with an initial negative component. During vagal escape (B) initial activity was recorded from the His bundle, the His complex was similar to the control in contour and polarity, and atrial activity from both the septum and the SA node followed...
His. The H-S interval was unchanged during the escape rhythm. Figure 3 (lower) shows records from another experiment in which the escape rhythm originated in the region of the A-V node, but in this case retrograde conduction into the atrium did not occur.

Figure 4 (upper) shows tracings from an experiment in which the vagal escape rhythm originated below the His electrode. During the control period (A) atrial depolarization preceded His and the His complex was diphasic in contour with an initial upward deflection. During the escape rhythm (B) the His complex was inverted and the H-S interval was shorter. The impulse was propagated retrograde through the A-V node with depolarization of the atrium after the ventricular complex. Although the anatomic position of the pacemaker cannot be defined with certainty, the inverted His potential indicates that the pacemaker was below the His electrode and that the impulse was transmitted in a retrograde direction. The marked reduction of the H-S interval suggests that the pacemaker was located in a relatively peripheral part of the ventricular conduction system. In figure 4 (lower) the escape pacemaker was again in the ventricle, but activity failed to propagate retrograde through the A-V node into the atrium.

**ISOPROTERENOL EFFECTS ON VAGAL ESCAPE**

The effects of vagal nerve stimulation prior to and during the infusion of isoproterenol were compared in 16 experiments on 8 animals. These observations are summarized in table 1.

The influence of isoproterenol on the time of vagal escape onset is seen in table 1 and tracings from two experiments are shown in figure 5. With the exception of one animal, isoproterenol consistently shortened the period of asystole prior to establishment of an escape rhythm. We have arbitrarily defined the onset of vagal escape as the establishment of a rhythmic pacemaker resulting in ventricular contractions at a rate of 16 to 20 per minute or faster.

The effect of isoproterenol on the maximal heart rate achieved during vagal escape is also shown in table 1 and in figures 5 and 6. In all instances in which escape rhythms were observed during both the control period and during isoproterenol infusion, the maximal rate of the escape mechanism was faster during the infusion. Isoproterenol increased the rate

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**FIGURE 4**

*Idioventricular escape mechanisms. Panel A = control. Panel B = vagal escape originating below the His electrode with retrograde conduction to atrium. Panel C = control. Panel D = vagal escape due to idioventricular rhythm with block of retrograde conduction to atrium. A = atrial septum, H = His bundle, S = interventricular septum. Electrical records retouched. (His electrogram only on this record.)*
TABLE 1

Effects of Isoproteonol on Time of Onset, Maximal Rate, and Pacemaker Mechanism of Vagal Escape

<table>
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<th>Expt. no.</th>
<th>Heart rate control</th>
<th>Vagal escape Onset</th>
<th>Vagal escape Rate</th>
<th>Mechanism</th>
<th>Heart rate control</th>
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<th>Rate</th>
<th>Mechanism</th>
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Onset = time interval between vagal stimulation and establishment of a rhythmic pacemaker; 0 = immediate escape. Rate = maximal rate achieved during vagal stimulation. Mechanism = pacemaker and rhythm; IV = idioventricular, SN = supranodal, AVN = atrioventricular nodal, 2:1 = second degree A-V block with 2:1 atrioventricular responses. Blanks represent no escape rhythm during 30 sec of vagal stimulation.
FIGURE 5
Effects of isoproterenol on vagal escape. AP = aortic pressure. Black bars = period of vagal stimulation. Upper panel: A = control prior to isoproterenol. Idioventricular escape at rate of 54 after 24 seconds of asystole. B = during isoproterenol, 2.2 μg/min. Immediate atrial escape with 4:1, then 2:1 A-V block at a rate of 71. C = control after isoproterenol. Lower panel: A = control prior to isoproterenol; three idioventricular beats, no regular escape rhythm. B = during isoproterenol, 1.6 μg/min. Idioventricular escape at a rate of 38 after 6 seconds of asystole. C = control after isoproterenol. Paper speed 2.5 mm/sec.

FIGURE 6
VAGAL ESCAPE

of the pacemaker regardless of its origin. Figure 6 shows that graded doses of isoproterenol produced a graded increase in the rate of an escape rhythm originating in the region of the A-V node.

In three experiments (no. 1,2,5) isoproterenol infusion changed the site of the escape pacemaker to a higher focus in the conduction system. In one experiment (no. 3) isoproterenol elicited a regular escape rhythm where only occasional idioventricular beats were observed during the control period. In three experiments (no. 14-16) isoproterenol either failed to elicit or appeared to suppress rhythmic pacemaker activity.

Discussion

The characteristic feature of cardiac fibers which exhibit the ability to act as pacemakers is spontaneous depolarization during the diastolic portion of the intracellular action potential. Fibers demonstrating this characteristic are found in the SA node,9 the sinoatrial ring,10 the lower A-V node,11 and in ventricular Purkinje tissue.12 Recordings from pacemaker fibers of supraventricular origin have shown that acetylcholine (or vagal stimulation) suppresses, while sympathetic amines enhance, diastolic depolarization.13 At the level of the A-V node, acetylcholine and sympathetic amines also exert contrasting effects on the action potential which delay and accelerate, respectively, A-V nodal transmission.14,15 Vagal stimulation can result in cardiac arrest either by abolishing pacemaker activity of supraventricular fibers or by blocking A-V conduction. Sympathetic agents would be expected to diminish the effects of vagal stimulation by increasing the rhythmicity of supraventricular pacemakers and by facilitating A-V conduction. In addition, sympathetic agents enhance spontaneous depolarization of ventricular Purkinje fibers16 and thereby increase the likelihood of idioventricular escape from vagal induced asystole.

This study was undertaken to localize the pacemaker areas responsible for vagal escape rhythms and to examine the effects of isoproterenol on escape mechanisms. The experiments have shown that vagal escape can result from the development of pacemaker activity in three general regions, above the A-V node, in the region of the A-V node, and below the common His bundle. Infusion of moderate doses of isoproterenol enhanced both the onset and rate of escape rhythms from each of these regions. It was also observed that isoproterenol improved A-V conduction, enhanced the automaticity of supranodal pacemakers, and thereby converted escape rhythms originating within or below the A-V nodal region to rhythms originating above the A-V node.

Supranodal rhythms during vagal escape were of two general types. In the first, initial activity was recorded from the SA node region during the control period and during vagal stimulation, the polarity and contour of the SA node and atrial complexes were unaltered, and the interval between them remained constant. These findings indicate that the pacemaker remained in the region of the SA node and that the escape rhythm was sinus bradycardia. In the second type of supranodal escape the pacemaker shifted to a different position, resulting in nearly simultaneous activation of the SA node and atrial septum. This observation indicates that the rhythmicity of the SA node had been suppressed by vagal stimulation and that escape resulted from a pacemaker area which was functionally equidistant from the SA node and the atrial septum.

Records from the atrium and His bundle demonstrated that in several instances pacemaker activity developed in the region of the A-V node during vagal escape. These rhythms were characterized by initial depolarization of His, a His complex identical in polarity and contour to that observed during the control period, and a normal interval between His and ventricular septum. These findings indicate that the pacemaker was above the His electrode. Depolarization of the atrium substantially after His, as well as complete block of retrograde conduction into the atrium in certain instances, indicate that the pacemaker was below the delay area in the A-V node. It seems likely, therefore, that the pacemaker was either in the lower A-V node or in the upper portion of the bundle of His.11
In several experiments vagal escape rhythms resulted from the appearance of a pacemaker located below the His electrode. This was characterized by variable shortening of the interval between His and ventricular septum and by a change in contour, inversion or complete absence of the His potential. In some cases these idioventricular beats propagated retrograde through the A-V node while in others retrograde transmission was blocked during vagal stimulation.

The importance of adrenergic factors in the phenomenon of vagal escape is suggested by reports that escape is more pronounced in species in which the myocardial catecholamine content is relatively high \(^1\) and by the observation that escape is retarded by adrenergic blocking agents or catecholamine depletion.\(^1\) Further, during vagal escape pacemaker activity can be promoted and enhanced by prior stimulation of the cardiac sympathetic nerves.\(^2\)

Isoproterenol is a sympathomimetic amine which has chronotropic and inotropic effects on the heart independent of myocardial catecholamine storage.\(^1\)\(^9\) This drug has found wide use in the treatment of complete heart block and Adams-Stokes attacks because of its ability to enhance idioventricular rhythmicity and A-V transmission.\(^2\)\(^0\)\(^2\)\(^1\)\(^2\) In view of the frequency with which vagal reactions are a cause of cardiac arrest as well as the possible influence of adrenergic factors on vagal escape, it was of interest to examine certain of the effects of isoproterenol on escape mechanisms.

Isoproterenol has been shown to elicit pacemaker activity in quiescent hearts,\(^2\)\(^5\),\(^2\)\(^6\) to increase the rate of both atrial and idioventricular rhythms,\(^2\)\(^0\),\(^2\)\(^7\) and to improve conduction through the A-V node.\(^2\)\(^1\),\(^2\)\(^8\) In the present series of experiments the influence of isoproterenol on the rhythmicity and conductivity of the heart was evaluated by examining the effects of this agent on vagal escape mechanisms. The observations that isoproterenol increased the rate of both atrial and idioventricular pacemakers, and converted rhythms originating within and below the A-V nodal region to supranodal mechanisms are consonant with the previous reports noted above. In addition, these experiments have shown that isoproterenol can increase the rate of rhythms originating in the region of the A-V node or upper His bundle. The effects of isoproterenol observed under these experimental conditions lend further support to the concept that the sympathetic nervous system may play an important role in the phenomenon of vagal escape. They also emphasize the potential usefulness of isoproterenol in the management of certain conduction disturbances resulting from vagal activity.

In three experiments the effect of isoproterenol was unusual in that the agent failed to elicit or appeared to suppress rhythmic pacemaker activity during vagal stimulation. Although isoproterenol has been reported to arouse ventricular pacemakers,\(^2\)\(^0\),\(^2\)\(^8\) its effect on ventricular automatism is generally considered to be slight in comparison to other catecholamines.\(^2\)\(^6\),\(^2\)\(^9\) Furthermore, Schwartz and Schwartz\(^2\)\(^4\) observed that isoproterenol occasionally slows the ventricular rate in complete heart block. These authors postulated that the positive inotropic effect of isoproterenol provided greater baroreceptor stimulation and thereby resulted in withdrawal of sympathetic nerve discharge to the heart with chronotropic inhibition. These considerations suggest that the occasional failure of isoproterenol to elicit pacemaker activity, as well as its apparent suppression of existing rhythmic sites, may have resulted from a relative lack of effect on automatism accompanied by reflex withdrawal of intrinsic sympathetic tone.

**Summary**

In dogs, bipolar electrograms were recorded from the SA node and His bundle to localize pacemaker sites during vagal escape and to study the effects of isoproterenol on escape mechanisms. Vagal escape can result from the development of pacemaker activity above the A-V node, within the region of the A-V node, and below the common bundle of His. Isoproterenol shortened the period of asystole prior to the onset of vagal escape, increased the rate of escape rhythms at all pacemaker sites, and occasionally changed the pacemaker to a higher focus in the conduction system.

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Pacemaker Activity During Vagal Escape Rhythms
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