Some Characteristics of Ventricular Echoes

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Two features of A-V transmission previously attributed to a dual conduction system; namely, "abnormal" delay in the A-V propagation of early premature atrial responses, and alteration of the configuration of the corresponding ventricular electrograms, have been adequately explained as due to aberrant conduction within the intraventricular conduction system, and more specifically as the result of block in the right bundle branch.

The most compelling evidence of intranodal dissociation has been the experimental demonstration of atrial and ventricular echoes. Reciprocal beats of the ventricle, triggered by premature ventricular contractions, have been described many times in the clinical cardiological literature (see, for example, Decherd and Ruskine, Kistin. Less commonly, atrial reciprocal beats have also been described. In the study by Moe et al., echo responses were attributed to two intranodal pathways having different refractory periods, permitting an early premature beat to pass from atrium to ventricle (or vice versa) over one pathway and return to the chamber of origin over the other. Rosenblueth presented similar evidence and conclusions, but he failed to observe echo responses in the atria. He therefore postulated two pathways, but assumed that one of the communications between atrium and ventricle was "polarized"; i.e., it could transmit impulses only from atrium to ventricle. He further postulated that a premature ventricular response must be propagated all the way back to the atria in order to result in a ventricular echo.

More recently, other features of A-V transmission have been interpreted in terms of intranodal dissociation. Moe et al. described an experiment in which a "paroxysmal" A-V nodal tachycardia could be induced in a dog's heart by premature stimulation of the atrium. The time relations of atrial and ventricular responses, the manner of induction, and the method of terminating the paroxysms pointed to reciprocal or "circus" movement activation through the A-V node as the most likely explanation of the dysrhythmia, a conclusion similar to that proposed by Barker et al. Although the possibility of experimentally induced, self-sustained, reciprocal rhythm had been considered earlier, it was predicted that the necessary combination of anatomic and physiologic conditions would not often concur. A more common event, also interpreted as an evidence of a dual A-V nodal transmission system, has also been observed. In these experiments, described as a "complex manifestation of concealed conduction," it was found that when an early premature response was induced in the atrium, its propagation to the ventricle appeared to be accelerated by the induction of a third atrial response. It was concluded that the third atrial response traversed the node over a pathway which had been unavailable to the second. Scher et al. also recorded events which were interpreted as reciprocation through the A-V node. These several independent observations suggest that the A-V transmission system can be readily forced to dissociate longitudinally. The phenomena have been demonstrated often enough to indicate that such dissociation is a normal property of the A-V node, not an unusual variant.
VENTRICULAR ECHOES

In all the experiments cited above, except those of Scher et al., direct recording of nodal activity was not achieved; the participation of the node was inferred from the temporal relations of atrial and ventricular responses to stimuli applied to the epicardial surface of the heart. As it has been reported that the refractory period of the intraventricular specialized conduction system is maximal at a level between the bundle of His and the ventricular myocardium, it is obvious that time intervals recorded at the atrial and ventricular surfaces may not provide an accurate estimate of the time course of impulse propagation within the node. Accordingly, the present study was undertaken, utilizing a modification of the open heart preparation described by Alanis et al., in order to appraise as closely as possible the role of the A-V node itself in the reciprocal propagation of impulses. Driving and premature stimuli, applied directly to the bundle of His, permitted the earliest possible premature penetration of the node; records of responses at the atrial margin of the node and at the His bundle defined the time attributable to intranodal transit. Other features of A-V transmission in some of the same animals have been reported previously.

Methods

The experiments were conducted on dogs prepared in a manner similar to that devised by Alanis et al., and described in greater detail in a previous study. The coronary circulation of a recipient animal was supplied with arterial blood from a donor animal. Both animals were anesthetized with pentobarbital, 30 mg/kg, administered intravenously. After heparinization of both animals, and after isolation of the recipient heart, in situ, the caval vessels were opened, permitting drainage of the coronary venous blood into the chest cavity, from which it was returned by gravity to an external jugular vein of the donor animal. The anterior wall of the right atrium was opened to expose the region of the A-V node and the bundle of His. Recording and stimulating electrodes in the form of bipolar steel needles were attached to the septal surface of the atrium close to the node, and two similar electrode pairs were placed on the bundle for recording and stimulating purposes. Recording electrodes were also attached to the epicardial surface of the right ventricle.

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Driving and test stimuli were rectangular pulses obtained from Tektronix pulse generators and passed through isolation transformers. The pulse generators were triggered from a series of push button delay units which permitted a sequence of 18 driving and test pulses at variable stimulus intervals. Responses were recorded on an Electronics for Medicine D-8 recorder at a paper speed of 100 mm/sec. Details of the stimulation sequences are described in the results.

Results

I. ECHOES INDUCED BY STIMULATION OF THE BUNDLE OF HIS

Ventricular echoes can be induced by premature stimulation of the ventricle, and they sometimes follow each basic ventricular stimulus, even when the basic driving frequency is quite slow. In either case, the necessary condition is a long V-A conduction interval. In the present study this condition was met by delivering premature stimuli to the His bundle at a time when retrograde propagation was delayed by the persistence of relative refractoriness in the A-V node. After each 16th driving stimulus (S1) a test shock (S2) was delivered through the same pair of electrodes at varying S1S2 intervals.

A ventricular echo induced by premature

FIGURE 1

Simultaneous bipolar electrograms recorded from three different locations in the perfused dog heart. Expt. 10-25-63. From above downwards: atrium in the vicinity of the upper node; bundle of His; right ventricular surface. In A the arrows S1 and S2 signal the moment of application of basic and test shocks to the bundle of His. The test response (H2) propagates to the atrium (A2) and an echo (H') returns to the bundle and ventricle (V'). The sequence of activation during the development of the echo is indicated by the dotted line. In B, stimuli applied to the right atrium. Interval between vertical lines, 100 msec.
stimulation of the bundle is illustrated in figure 1A. The first trace was recorded from atrial muscle adjacent to the upper margin of the A-V node. Because of the proximity of these electrodes to the interventricular septum the depolarization of this tissue also appears in the record. The second trace was recorded from the proximal portion of the bundle of His above, but close to, the stimulating electrodes; activity of atrium and ventricle appears in addition to the His potential. The identification of each of these complexes has been previously established. The third trace was recorded from the epicardial surface of the right ventricle. The arrow marked Si signals the shock artifact of the last basic stimulus. The resulting response (H) was propagated to the atria and ventricles as A and V, with conduction intervals of 64 and 42 msec, respectively. When the test shock S2 was applied, 265 msec after Si, the resulting H2 response was also propagated to the atria, but the H2A2 conduction time was 145 msec. The H2V2 interval was only slightly longer than H1V1 and therefore the auricular and ventricular components recorded in the second trace are now clearly separated. Following A2 a recurrent His response, H', was recorded; it propagated to the ventricles as a ventricular echo (V'). The polarity of H' is inverted with respect to the stimulated H1 and H2 responses because the stimulating electrodes were located distal to the recording pair. Figure 1B shows the traces obtained in the same experiment when the heart was driven by stimuli applied to the atrium. The position of the recording electrodes was not changed; the polarity of the atrial responses is reversed, but the His and ventricular responses have the same polarity and configuration as the H' and V' deflections in figure 1A.

II. ECHO ZONE

Echo responses could be obtained by premature stimulation of the His bundle in the majority of preparations. In each successful experiment, there was an echo "zone"; that is, a continuous range of H1-H2 intervals within which H2 was regularly followed by return impulses. The duration of the echo zone varied considerably from experiment to experiment, from a very brief and critical period up to 85 msec. The earlier limit always corresponded to the shortest H1-H2 interval with which H2 propagated to the atrium. This interval, which will be called the shortest effective H1-H2 interval, was usually appreciably longer than the functional refractory period of the His bundle itself. The ultimate limit of the echo zone was determined by the speed of retrograde propagation; i.e., echoes were obtained only when the H2A2 conduction time exceeded a critical value.

It was possible, in the majority of the experiments, to stimulate the bundle so prematurely that H2 failed to reach the atria. In these conditions, in agreement with Rosenbluth,7 no return beats occurred.

Estimation of the duration of the echo zone is illustrated in figure 2. The stimulated His responses follow closely upon the shock artifacts and cannot be separately discerned in the figure. In figure 2A, the H1H2 interval was 285 msec; H2 propagated to the ventricles but did not reach the atria and was not followed by an echo. In B, H1H2 (305 msec) was the shortest effective interval; A2 was followed by an echo, H'. In C, H1H2 (360 msec) was the longest interval still followed by an echo and it will be termed the longest effective H1H2 interval. In D, at a slightly longer interval (364 msec), no echo occurred. The limits of the echo zone in this experiment are defined by the H1H2 intervals in parts B and C of figure 2. At the shortest effective interval, the retrograde propagation of H2 was slow (H2A2, 279 msec) but the A2H' interval was brief (54 msec); at the longest effective interval the H2A2 interval was reduced to 190 msec, while the corresponding A2H' interval had increased to 103 msec.

All the H1H2 intervals within the echo zone were followed by return impulses in every experiment. Plotted in figure 3 are the temporal relationships between H1H2 (abscissa) and the corresponding H2A2, A2H' and H2H' intervals obtained in one of the experiments. The horizontal bar defines the echo zone. As the H1H2 interval was increased from the
earliest effective interval, the $H_2A_2$ interval decreased. This was the expected result of recovery of excitability in the retrograde conduction pathway. The $A_2H'$ intervals, however, increased; the highest value was recorded at the longest effective $H_1H_2$ interval. The $H_2A_2$ and $A_2H'$ curves obviously determine the $H_2H'$ curve; because of their shape $H_2H'$ goes through a minimum. The upper curve shows that during a portion of the echo
zone the $A_1A_2$ intervals remained nearly constant; these values increased, however, at both extremes of the zone. Not all such curves passed through a minimum. In some experiments, only the right-hand limb of the $H_2H'$ curve was apparent, for when $H_1H_2$ was diminished the propagation of $H_2$ to the atrium failed before very long $H_2A_2$ intervals occurred. In others, only the left-hand limb was present, for on occasion a sharp discontinuity appeared in the curve relating $H_1H_2$ to $H_2A_2$; under these circumstances the $A_2H'$ was not greatly prolonged prior to the break in the curve. Figure 4 shows one of these cases. As the $H_1H_2$ interval was decreased from 466 msec to 404 msec the corresponding $H_2A_2$ intervals increased continuously, but a further decrease of only one msec caused an abrupt increase of the $H_2A_2$ interval. This discontinuity was, of course, reflected in the $A_1A_2$ curve. Further abbreviation of $H_1H_2$ was accompanied by a progressive increase of $H_2A_2$ until $H_2$ failed to reach the atrium. The echo zone in this experiment did not extend beyond the discontinuity at 403 msec; with one exception this was true of all preparations in which a discontinuity was observed.

In some preparations, it was not possible to obtain echoes. A common feature in these cases was that the maximal $H_2A_2$ intervals obtained were considerably shorter than those recorded in successful experiments. In other words, as $H_1H_2$ decreased, $H_2A_2$ increased smoothly, but retrograde propagation failed before sufficiently long $H_2A_2$ intervals were achieved. On occasion, a preparation behaved in this fashion at the beginning of the experiment but permitted the development of echoes at a later time.

III. ROLE OF THE ATRIUM IN THE PRODUCTION OF ECHOES

Rosenblueth postulated that the atrium participates in the echo phenomenon. In other words, the echo beats return from the atrium and not from a loop within the A-V node. This conclusion was based on the fact that the ventricular impulses which were followed by echoes always reached the atrium; when retrograde propagation failed, the echoes disappeared. The evidence, although suggestive, is not definitive. The possibility exists that in order to provoke an echo a retrograde impulse must first cross the zone with lowest margin of safety. If this zone is within the node any retrograde impulse followed by an echo must also reach the atrium, but the return beat might actually start below it. For these reasons, experiments were designed to determine whether or not the atrium is an essential link in the genesis of echoes.

In the sequence of $H_2A_2-H'$ some elements, including the His bundle, must fire twice in succession. Therefore a likely explanation for the progressive increase of the $A_2H'$ intervals observed when the $H_1H_2$ interval is prolonged (and $H_2A_2$ is correspondingly abbreviated) is that, somewhere in their path, the return beats encounter tissue progressively more refractory; at the longest effective $H_1H_2$ interval.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4}
\caption{Relationship of $A_2H'$, $H_1A_2$, $H_2H'$, and $A_1A_2$ intervals to $H_1H_2$ intervals in an experiment in which a discontinuity occurred. Expt. 10-24-63. Scales and symbols as in figure 3. Echoes did not occur to the right of the break in the $H_1A_2$ curve.}
\end{figure}
the return beat must barely escape extinction at a refractory barrier. In other words, the conduction time of the return beat must be determined by the stage of refractoriness persisting in that portion of the pathway common to both legs of the journey. When $H_1H_2$ is brief, and $H_2A_2$ is therefore prolonged, complete recovery of the common segment may occur, while at longer $H_1H_2$ intervals the propagation of the echo will be correspondingly delayed. If this is true, and if the atrium is an essential link in the pathway, then at short $H_1H_2$ intervals it should be possible to pre-excite the atrium (in advance of the expected arrival of $A_2$) and find a pathway available for propagation to the His bundle. If this pathway is indeed fully recovered, then the resulting His response should be coupled to the induced atrial response with an $AH$ interval equal to the $A_2H'$ interval. Conversely, if the propagation of the echo at the longest effective $H_1H_2$ interval barely escapes extinction at a refractory barrier, then pre-excitation of the atrium just prior to the expected arrival of $A_2$ should cause the disappearance of the echo and should fail to cause a response of the His bundle.

In the experiment illustrated in figure 5 these predictions appear to be confirmed. Figure 5A shows an echo obtained with the minimal effective $H_1H_2$ interval. In part B, the interval was the same, but the atrium was stimulated at the moment indicated by the arrow $S_3$. The resulting response was recorded 125 msec in advance of the expected arrival of $A_2$, and it presumably crossed the node giving rise to $H'$. The assumption that $H'$ resulted from $A'$, and was not an echo response to $H_2$, is based on the time relations of the respective responses. The $H_2H'$ interval in figure 5B was 12 msec less than the $H_2H'$ interval in figure 5A. Earlier positions of $A'$ blocked the echo response, but were not accompanied by His responses. An echo obtained with the longest effective $H_1H_2$ interval in the same experiment is illustrated in figure 5C. The $A_2H'$ interval was 103 msec, as compared with the value of 54 msec recorded in figure 5A. If the postulates outlined above are valid, no earlier $A_2$ response should succeed in traversing the node. This was tested, as shown in figure 5D, by inducing a stimulated response, $A'$, just 8 msec in advance of the expected retrograde response $A_2$. This slightly premature atrial response prevented the emergence of the echo, and failed to propagate to the His bundle.

The results of pre-excitation of the atrium were studied in several experiments in which the position of $S_3$ was varied in steps of 5 or more milliseconds at several fixed $H_1H_2$ intervals within the echo zone. The results obtained in one of these experiments are illustrated in figure 6. The abscissae represent time in milliseconds. In each section the ordinate represents distance across the A-V region on an arbitrary scale. The upper horizontal dotted line in each segment of the figure represents the junction of the atrium with the
Effects of premature atrial responses elicited during the development of echoes. Expt. 10-1-63.

Abscissae: time in msec. Ordinates: distance across the A-V region (arbitrary scale). The A-V node (A-VN) is separated from the atrium (A) and the bundle (H) by the horizontal dotted lines. The propagation of H to the atrium and its return as an echo are represented by the continuous lines joining H to A and A to H'. The premature atrial responses (evoked in the presence of H) are represented by the broken vertical bars A', and the corresponding His responses by the broken bars H'. In A and C, H, corresponds to the shortest and longest interval followed by an echo, respectively. In B, H, has an intermediate value. In each segment the earliest A' response shown does not propagate to the bundle, but it causes the disappearance of the echo.

Upper portion of the A-V node and the lower dotted line represents the junction between the distal portion of the node and the bundle of His. H, represents the last basic His response and A, the corresponding atrial response recorded in the immediate vicinity of the node. In segment A of the figure, H, was fixed at 295 msec, corresponding to the shortest effective interval. The premature H, response propagated slowly to the atrium and returned to the His bundle as an echo (H'). Although the H, interval was fixed, the position of A, was not constant. H,A, varied within a range of 15 msec, but the A,H' interval was constant; the temporal positions of A, and of H' in the figure correspond to the earliest time these responses were recorded. In the presence of H, the atrium was pre-excited at various intervals before the expected arrival of A,. The stimulated atrial responses are represented by the broken vertical bars labelled generically A'. These responses were easily identified by their configuration and their constant relation to the corresponding shock artifacts. The A' responses were followed by His responses, also represented by vertical broken bars labelled H'. The latest A' response shown was recorded 8 msec in advance of the expected arrival of A, and the corresponding H' response preceded H' by a similar interval. In other words, the latest A'H' interval was equal, as predicted, to the A,A' interval. The same A'H' interval was also recorded for the immediately preceding A' response, and only slight increments in A'H' occurred as A' was initiated still earlier up to about 500 msec. Earlier A' responses were propagated with increasing delay, but the resulting H' responses were displaced to the left up to a
limit, at which point H' preceded the H' response by 83 msec. Once this limit was reached a further shift of the A' response caused a displacement of the H' responses in the opposite direction until the earliest A' response shown in the figure failed to propagate to the bundle. There was a range of 144 msec during which A' responses, initiated in advance of A2, could be propagated to the bundle. Within this range the A'H' response must have taken a pathway which, at least in the upper portion of the node, was not engaged by the H2A2 response.

In part B of figure 6, the H1H2 interval was 323 msec. The time of appearance of A2 was now essentially fixed. The H2A2 interval was shorter than in part A but the A2H' interval was longer. The range during which A' was able to propagate to the bundle decreased to 52 msec. As in part A, the latest A' response shown arrived at the bundle before the previously recorded H'; the A'H' interval was essentially equal to A2H'. In figure 6C, H1H2 was 362 msec, the longest effective interval in this experiment. The H2A2 interval was shorter than in segment B, but the A2H' interval was considerably prolonged. The A' response shown in the figure preceded the expected arrival of A2 by 7 msec, blocked the echo, and failed to propagate through the node.

In the same experiment H1H2 intervals slightly shorter than 362 msec permitted a small range of A' responses, which propagated to the bundle. In these conditions, the H' response evoked by the latest A' response occurred later than the previously recorded echo.

The results obtained in figure 6A suggest that the return beat propagated in tissue fully recovered, for the A2H' interval was equal to the A'H' interval of the latest two stimulated atrial responses. If this is true, then the propagation of A' to the His bundle should not be influenced by the presence of H2. A test of this assumption is illustrated in figure 7. In part A an echo was evoked with the shortest effective H1H2 interval. In part B, H2 was omitted, but the atrium was stimulated at the time signaled by S2, yielding an A1A2 interval slightly briefer than that recorded in figure 7A. The A2H' and A2H2 intervals were essentially equal; it is apparent that any portion of the echo pathway invaded by H2 must have been fully recovered by the time it was re-engaged by A2. It also follows from this series
Comparison of the shortest $H_2H'$ interval with the
of observations that the echo circuit must indeed have included the atrium as an essential link as postulated by Rosenblueth.  

IV. REFRACTORY PERIOD OF THE RETURN PATH

When echo responses occur some elements of the atrio-His transmission system are activated not only by the retrograde propagation of $H_2$, but also by the return impulse. Since these elements fire twice in succession, their refractory period (RP) might tax and perhaps limit the propagation of the echo beats. In support of this hypothesis it has already been mentioned that within the echo zone, the $A_2H'$ interval increases and reaches its highest value at the right extreme of the zone. The curve relating the $H_1H_2$ and $H_2H'$ intervals has, in general, a minimum (fig. 3) and the shortest $H_2H'$ interval obtained can be considered as a rough estimate of the functional refractory period of the elements common to both propagations.

It was suggested by Rosenblueth that the bundle of His is the element whose refractory period limits the propagation of the echo responses. This possibility was tested directly in several experiments, one of which is illustrated in figure 8. In part A, the $H_2H_1$ interval (equal to $S_2S_1$) was chosen to give the briefest possible $H_2H'$ interval; i.e., the interval determined by the RP of the common element. In parts B and C, the $H_1H_2$ interval was the same, and the RP of the His bundle following the $H_2$ response was assessed by the direct application of $S_3$ stimuli. In figure 8B, $S_3$ generated a response of the bundle 40 msec in advance of the expected arrival of the echo, $H'$. In part C, $S_3$ was delivered 10 msec earlier; it failed to generate an $H_3$ response, and therefore failed to prevent the echo. In this experiment, the functional refractory period of

**FIGURE 8**
Comparison of the shortest $H_2H'$ interval with the

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Functional refractory period of the bundle. Expt. 10-1-63. Records as in figure 1. In A, $S_1S_2$ interval chosen to give the shortest $H_2H'$ possible. In B, $S_2S_3$ same as in A; a third shock $S_3$ successfully stimulates the bundle considerably in advance of the expected arrival of $H'$. In C, $S_3$ applied 10 msec earlier than in B, fails to stimulate the bundle and an echo similar to the one obtained in A is recorded.
the bundle was 40 msec less than the shortest possible H2H' interval. In other experiments, the difference was as great as 70 msec. It is safe to conclude that the refractory period of the bundle itself does not limit the propagation of echoes; the refractory period of the return path must be determined by elements which are located within the node itself.

The same elements which limit the propagation of the echo response must also appose the barrier to transmission of the pre-excited atrial responses (A' in fig. 6). Accordingly, the propagation of A2H' (the echo response) and the propagation of A'H' should follow the same set of rules. At any given H1H2 interval within the echo zone, the H2H' and H2H' intervals should fit the same curve when plotted against the H2A2 (or H2A') intervals, and when similar relationships are plotted for different positions of H2, the several curves should be members of the same family, differing only by the expected frequency-dependent alteration in the functional refractory period of the limiting element imposed by the different preceding cycle lengths (H1H2).

These assumptions were tested in several experiments designed to provide an estimate of the refractory period of the limiting element in the echo pathway. In figure 9A, H2H' is plotted as a function of H2A2 for three different H1H2 intervals, including the shortest effective interval (H1H2 = 295 msec) and the interval (H1H2 = 334) which yielded the minimum H2H' interval.* Echo responses are indicated by the open symbols; responses to pre-excitation of the atrium (A') in each series are indicated by the corresponding filled symbols. The three sets of data (and other sets not plotted in the figure) are tightly grouped; the minimal H2H' values recorded in each set fall within a range of only 10 msec, which probably represents actual differences in the refractory period as a result of the alteration in the preceding cycle length in the three sets of observations.

Related data from the same experiment are

*It is perhaps not obvious why the H2A2 (or H2A') interval was chosen for the comparison plotted in figure 9A. Numerous temporal positions of the atrial responses to direct stimulation (designated as A') were to be compared with the atrial responses propagated from the His bundle (designated as A2) at several fixed H1H2 intervals. To assess the RP of the limiting elements, it was necessary to determine the minimal H2H' interval for each position of H2. This was accomplished by scanning with A'; as A' is delivered progressively earlier in such a series, the H2H' interval must reach or pass through a minimum value, just as in the estimates of A-V nodal functional RP described by Krayer et al.15 Consequently, the independent variable in each curve is the position of A' relative to the fixed point (H2) which defines the beginning of the RP in each case. The lower curve of figure 9B was then constructed to show these minimal H2H' intervals as a function of the preceding cycle length (H1H2) as the independent variable.
presented in a different form in figure 9B. Here, the H₂H' intervals (open circles) are plotted, as in figure 3, as a function of the H₁H₂ interval. The curve goes through a minimum at H₁H₂ = 335 to 345 msec. At H₁H₂ intervals of 345 msec and longer, no earlier response of the His bundle could be evoked by pre-excitation of the atrium. At shorter H₁H₂ intervals, the propagation of H₂A₂ was delayed, and A' responses reached the His bundle earlier than the corresponding echo responses. The resulting minimal H₂H' intervals are indicated by the filled circles; they are presumably determined by the refractory period of the limiting element in the node, and they show the expected relationship between RP (as estimated by the minimal H₂H') and preceding cycle length (H₁H₂).

It is possible that when H₂ is delivered too early to reach the atrium (H₁H₂ intervals less than the shortest effective interval) it nevertheless enters the node and discharges the common element within it. This is suggested by the left-most point in the curve of figure 9B. At an H₁H₂ interval of 284 msec, the minimal H₂H' interval obtained upon stimulation of the atrium was just 5 msec less than that recorded when H₂ was placed at the earliest moment when it could be propagated to the atrium.

The schematic basis for these conclusions is illustrated in figure 10, based on values recorded in the experiment from which figure 9 was obtained. In part A of the figure, H₂ was placed in the latest position at which it failed to propagate to the atrium (H₁H₂ = 284 msec). It is represented as entering and discharging the common element in the lower node. A scan with S₈ applied to the atrium revealed a minimal H₂H' interval of 264 msec, and an A'H' conduction interval of 81 when A' was initiated at the time shown in the diagram. In the absence of H₂, A' propagated at full speed (dotted line). Pre-excitation of the atrium at the time which resulted in the briefest attainable H₂H' interval is indicated as A'. In the absence of H₂, this response would also have propagated to the ventricle at full speed. Accordingly, it must be assumed that that portion of the intra-nodal pathway not engaged by H₂ was fully recovered by the time A' was initiated. Its passage is therefore represented as a straight line with a slope.

FIGURE 10
Schematic explanation of events displayed in figure 9. Expt. 10-1-63. A: H₁ placed just too early to propagate to atrium, enters and discharges common element in lower node; RP of that element indicated by shading. Minimal H₂H' interval was observed when A' placed in position shown. In absence of H₁, A' propagates at full speed (dotted line). B: H₁H₂ at shortest effective interval leads to echo propagated at full speed from atrium to His bundle (A₁H'). A' in position indicated yielded minimal H₂H' interval. C: H₁H₂ at longest effective interval; no earlier response of His bundle than H' could be elicited by pre-excitation of atrium. Time scale dates from H₁.
parallel to that of $A_2H'$ down to the point
where it is assumed to be delayed at the
refractory barrier of the common element. In
figure 10C, taken from the series of observa-
tions which defined the minimal $H_2H'$ inter-
val, no earlier response of the atrium than
that indicated by the position of $A_2$ could re-
sult in an earlier response of the His bundle.

The construction diagrammed in figure 10
does not, of course, permit a precise estimate
of the effective refractory period of the limit-
ing element in the $H_2-A_2-H'$ sequence; the
minimum $H_2H'$ intervals indicated include
the RP plus the conduction time in both di-
rections within the common element. In the
figure, the postulated duration of the refrac-
tory period is 210 msec in part B ($H_1H_2 = 295$
msec) and 220 in part C ($H_1H_2 = 345$ msec).
The depth of penetration of $H_2$ in the common
element is represented to be the same in both
cases. While this assumption cannot be rigor-
ously defended, it is likely that, had the later
$H_2$ penetrated a greater distance, then the
minimum $H_2H'$ interval should have increased
more steeply than was actually observed as
$H_1H_2$ was prolonged.

V. INFLUENCE OF FREQUENCY
UPON THE ECHO PHENOMENON

The apparent refractory period and the
conduction time of the A-V transmission sys-
tem are frequency-dependent variables. In
the preceding section it was shown that the
dimensions of the echo zone are critically de-
pendent upon the $H_2A_2$ and $A_2H'$ conduction
intervals and upon the RP of the limiting ele-
ment in the return pathway. Echoes cannot
occur unless the retrograde conduction time
is long enough to permit recovery of excitabil-
ity in the return route. At an increased basic
driving frequency one might expect a pro-
longation of the $H_2A_2$ interval and an abbrevi-
ation of the RP in the common limb of the
pathway. Both of these alterations should be
expected to favor the occurrence of echoes.

The influence of frequency, subjected to
study in several experiments, is not quite so
simple as conjectured. One of these experi-
ments is plotted in figure 11, using the same
format as that of figure 3. The $A_2H'$, $H_2A_2$,
and $H_2H'$ intervals at a basic cycle length of
800 msec are plotted as ordinates against $H_1H_2$ in column B, and the same parameters
at a basic cycle length of 540 msec in column
C of the figure.

A number of apparently paradoxical fea-
tures of the comparison presented in figure 11
require interpretation. First, the echo zone is
shifted bodily to the right by acceleration of the
basic driving frequency. The earliest $H_2$
response which was able to propagate back to
the atrium, and which therefore defines the
shortest effective $H_1H_2$ interval, was shifted
from 352 msec to 427 msec. Second, the mini-
mal $H_2H'$ interval, already shown to be deter-
mimed in large measure by the limiting RP in
the return pathway, was increased by about
10 msec at the higher frequency. Finally, the
shortest $H_2A_2$ conduction interval which still
permitted echo responses was increased by
about 15 msec. These results are not, how-
ever, incompatible with the postulates enu-
merated above. Echoes cannot occur unless
$H_2$ reaches the atrium. The temporal shift of
the echo zone is accounted for by the fre-
quency-related depression of retrograde con-
duction. The increase in the $H_2H'$ interval at
the higher frequency is in fact not a paradox,
for the RP of the limiting element must be a
function of the immediately preceding cycle
length. At the higher frequency, the $H_1H_2$
interval, which is the preceding cycle for the
element in question, was not in fact reduced,
but was increased by about 75 msec. As a re-
sult of this effect, the shortest $H_2A_2$ interval
which still permitted the reflection of echoes
was somewhat prolonged.

VI. INFLUENCE OF EPINEPHRINE

The effect of epinephrine upon the tem-
poral relationships within the echo zone is
also shown in figure 11 as the data plotted in
column A. The very profound effects of this
agent are evident upon comparison of col-
umns A and C, both recorded in the same
experiment at the same basic cycle length of
540 msec. The duration of the echo zone was
changed very little, but as a result of the
greatly improved retrograde conduction, the
shortest effective $H_1H_2$ interval was reduced
Effect of driving frequency and of epinephrine infusion on temporal relationships of echo zone.
Expt. 6-26-64. Symbols and scales as in figure 3. Column A: basic cycle length 540 msec; epinephrine infused at rate of 1.0 μg/min. Column B: basic cycle length 800 msec (no epinephrine). Column C: basic cycle length 540 msec (no epinephrine). Note break in abscissa between 300 and 360 msec.

Figure 11

VII. INFLUENCE OF VAGAL STIMULATION

A-V conduction times and the functional refractory period are increased by vagal stimulation; retrograde conduction is particularly sensitive. Accordingly, only very moderate intensities of vagal stimulation could be studied. In the experiment illustrated in figure 12, mild stimulation of the right vagus nerve shifted the echo zone to the right. The earliest $H_2$ able to propagate to the atrium was shifted from 322 to 368 msec. The RP of the limiting elements in the return pathway could not be estimated, for the $H_2H^*$ curve did not long $H_2A_2$ intervals were reached. Under these conditions it was sometimes possible to evoke echo responses by infusing epinephrine at rates sufficient to abbreviate the RP of the limiting elements.
Effect of vagal stimulation on echo zone. Expt. 6-8-64. Symbols as in figure 3. Basic cycle length 500 msec; for control observations (left-hand column) and also for observations recorded during mild stimulation of right vagus nerve (right hand column).

Discussion

Point of reflection of ventricular echoes

In section III we have discussed the evidence which led Rosenblueth to postulate that ventricular echoes return from the atrium. The same hypothesis was adopted by Scher et al., but their records do not exclude the possibility that the return beats may actually start inside the A-V node.

The results presented in section III demonstrate that the atrium plays an essential role in the genesis of echoes. If it be assumed that they return, not from the atrium, but from some point within the A-V node, then once an echo is reflected, the path it takes to the bundle will not be available to atrial impulses. Therefore, in the situation shown in figure 6A we should not expect the late A' responses to modify the position of H'; earlier positions of A' could, of course, reach the return route before its engagement by the retrograde H2 and therefore propagate successfully to the His bundle. But even the latest A' was followed by an H' response which preceded the anticipated arrival of H'. The same argument can be applied to the results illustrated in figure 6B. In part C of the same figure, if the return impulse started inside the A-V node (i.e., in advance of the appearance of A2) it would not have been possible to block it with an atrial response generated just prior to the expected arrival of A2. It is important to emphasize that these results (fig. 6C) were possible only in those experiments in which the A2H* conduction interval was very prolonged; i.e., when the return of the echo response was clearly encumbered or even temporarily arrested by refractory tissue in the lower reaches of the node. Under these conditions any earlier atrial response would be expected to fail to excite the final common pathway. In those experiments in which the right extreme of the echo zone coincided with discontinuity in the H2A2 curve (fig. 4), the propagation of A2H* at the longest effective H1H2 interval was not severely encumbered by the persistence of refractoriness in the return pathway; A' responses initiated in advance of A2 under these circumstances were propagated to the His bundle.

The results obtained in experiments of the type illustrated in figure 7 provide further evidence that the echoes return from the atrium. In these experiments, the A3H* delay of the echo beat could be equal to but never shorter than the corresponding delay of normal orthodromic impulses travelling in tissue fully recovered. These data also suggest that the route taken by the echo beats from atrium to bundle was the same as that followed by normal impulses. Results comparable to those
shown in figure 7 were obtained in three additional experiments in all of which the H2A2 conduction time at the shortest effective H1H2 interval was extremely prolonged, thereby providing time for essentially full recovery of excitability in the return pathway. In other experiments, in which the maximal H2A2 interval was less prolonged, the A2H* interval was longer than the conduction time of normal orthodromic impulses.

In summary, it is safe to conclude that whatever the H1H2 interval employed to obtain an echo, the atrium is always an essential link in the path.

MECHANISM OF VENTRICULAR ECHOES

Three possible mechanisms must be considered:

1. It is conceivable that the echoes do not arise from a continuous propagation of the premature retrograde activity, but are actually spontaneous responses. According to this hypothesis, we would assume that the premature His response, although blocked inside the A-V node, somehow induces a spontaneous discharge above the level of the block. In those cases in which very long H2A2 intervals were recorded (nearly 300 msec at the shortest effective H1H2 interval in figure 3, for example), it is conceivable that the A2 response was not propagated from the His bundle at all, but originated somewhere within pacemaker tissue above a site of block of the H2 response. The S-A node could not have been the generator, for the S-A node was routinely destroyed in all experiments. As judged by the temporal relationships between atrial and His bundle responses, spontaneous activity, when it was allowed to appear, was always initiated within the A-V node or below it. But the hypothetical spontaneous source of A2 could not be in the A-V node, for we have already shown that the echo responses must always return from the atrium. We would be forced, then, to suppose that a retrograde response, dying within the A-V node, arouses a dormant pacemaker within the atrium; and that this pacemaker fires only when a blocked retrograde response occurs. This seems highly improbable. Furthermore, in the many experiments in which the H2A2 intervals increased continuously as the H1H2 intervals decreased (Figs. 3 and 11) it seems likely that the A2 responses were not spontaneous beats but were the result of the retrograde propagation of H2. As Rosenblueth7 pointed out, the transition from successfully propagated impulses to spontaneous activity should be accompanied by a discontinuity in the curve relating these events.

2. In the rabbit and dog heart, Matsuda et al.,17 Paes de Carvalho and de Almeida,18 and Hoffman et al.12 have described considerable delays in the activation of some nodal cells. If in the propagation of early retrograde impulses to the atrium there is a region where an impulse stops and propagation is resumed only after a considerable delay, it is conceivable that the delayed action potential could re-excite the previous elements. This would result in an echo. However, since the atrium is necessary for the production of echoes the above mentioned delay could take place only at the junction of the upper elements of the node with the atrium. In section III, it was shown that with the shortest effective H1H2 interval, the return beat may propagate in fully recovered tissue (Figs. 6 and 7). Therefore, the hypothesis under consideration would only be tenable if the latency involved were longer than the total duration of refractoriness, including the relatively refractory period, of the upper elements of the node. In other words, this would imply that an element A can stimulate the next element B after the action potential of A has disappeared. If the propagation of impulses is electrically mediated, latencies of this magnitude seem unlikely.

3. The hypotheses considered above do not postulate a longitudinal dissociation of the A-V node, but they do not adequately explain the genesis of echoes. The hypothesis that follows is similar in certain respects to earlier suggestions.1,7,11 Let it be assumed that shortly after a premature His response enters the node it fails at some site, but continues to propagate through others. Let it be further assumed that once the dissociation starts, lat-
eral propagation within the node is not possible. It follows that one longitudinal band of nodal tissue will not be invaded by the retrograde propagation of the premature impulse. This band, extending up to the atrium, will provide a return path once the atrium is activated by the retrograde propagation of $H_2$. An echo will successfully reach the bundle if it finds the tissue below the region of dissociation sufficiently recovered. The time allowed for recovery of this region will be given by the interval between the moment the retrograde $H_0$ arrived at the junction, and the moment the reflected impulse returns. Presumably, this interval must increase as the retrograde conduction time ($H_1A_2$) increases. Consequently, since the shortest effective $H_1H_2$ interval can provide quite long $H_2A_2$ intervals, the return beat may propagate back to the bundle without delay at the junction (figs. 6A and 7). As $H_1H_2$ increases, the propagation time of the premature beat to the atrium will decrease. As a result, the return beats will find the region below the point of dissociation progressively more refractory until finally the echoes will fail to propagate to the bundle. The hypothesis thus provides an explanation for the progressive increase of $A_0H_0$ observed when $H_1H_2$ increases (fig. 3).

The experiments described in section III (fig. 6) provided a situation in which two impulses travelling in opposite directions did not collide and extinguish each other; one of them was able to complete its journey. This case can also be explained readily in terms of longitudinal dissociation within the node: the stimulated atrial responses ($A'$), initiated in advance of the expected arrival of $A_2$, will penetrate the pathway open to the retrograde progress of $H_2$ and collide with it; but the premature atrial responses will also engage the band of tissue not invaded by $H_2$ and will propagate to the bundle if they find excitable tissue in their course through the lower node.

The assumption that lateral propagation inside the node is not possible above the region of dissociation is essential, for otherwise the return impulse would short circuit within the node. It is not absolutely necessary to postulate two anatomically separate and insulated pathways. Woodbury and Crill have shown that propagation of atrial impulses in a direction perpendicular to the longitudinal axis of the fibers is considerably taxed. Since the margin of safety in the A-V node seems to be considerably lower than in the atrium, failure of lateral propagation in some regions of the node at least during the relatively refractory period is perhaps mandatory.

The assumption, that within the echo zone $H_2$ blocks at some site in the node while it continues to propagate through others, merits consideration. In the preparations which provided a wide echo zone, the latest $H_2$ still followed by an echo, was propagated to the atrium at less than full speed, but it was nevertheless far short of complete failure. In figure 3, for example, the $H_2A_2$ conduction time at the longest effective $H_1H_2$ interval was about 175 msec, but the earliest $H_2$ was propagated with an $H_2A_2$ interval 120 msec longer. If we assume that even the latest effective $H_2$ blocks at some site in the node, it is necessary to postulate that there is a region which always fails to transmit retrograde impulses, or that it fails when the excitability of tissue is only slightly depressed. However, the same region must transmit forward impulses in tissue considerably refractory. Therefore, the hypothetical site of retrograde block must be completely "polarized" in favor of orthodromic conduction, or at least more nearly polarized than other parts of the node. The precise location of the assumed junction is, of course, not known. However, it must be inside the node. If it were at the junction of the bundle with the node, the refractory period of the bundle itself would limit the propagation of the return beat. This was shown not to be true (section IV; fig. 8). It should be emphasized that the evidence which places the barrier within the node does not require that the RP of this element exceed that of the bundle of His. The schematic diagrams of figure 10 illustrate that the site of delay or block of echo responses can be within the node even if the RP of the common segment is equal to or less than that of the His bundle.

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Previously published studies indicate, in fact, that the earliest premature response of which the His bundle is capable penetrates the A-V node.\textsuperscript{10}

It is possible that the site where dissociation occurs is the same whatever the temporal position of $H_2$ within the echo zone. In figure 9A, as already mentioned, the minimal $H_2H'$ value of each curve represents a rough measure of the functional refractory period of the elements common to the retrograde propagation and to the echo. When the parameter $H_1H_2$ was decreased, the minimal $H_2H'$ interval decreased slightly (fig. 9B). The site of block could, however, be the same in all cases; the slight displacement of the curves could be the result of the well-known effect of cycle length on refractory period.

Rosenblueth\textsuperscript{7} postulated that echo impulses return to the bundle through a hypothetical synaptic or ephaptic junction between atrial muscle and the common bundle. He assumed that this junction is completely "polarized," permitting the passage of orthodromic impulses only, and that the refractory period of the bundle would limit the propagation of the return beats. In section IV it was shown that it is not the RP of the bundle which limits the propagation of the return impulses. Accordingly, Rosenblueth's hypothesis is not tenable; but his general conclusions that (1) the necessary and sufficient condition for the production of echoes is a long V-A conduction interval, and (2) the atrium is an essential part of the echo pathway, are fully substantiated by the present study.

**POSSIBILITY OF SELF-SUSTAINED RECIPROCAL ACTIVITY**

Recirculation through the A-V node has long been considered as a likely explanation for paroxysmal A-V nodal tachycardia in the human subject (see, for example, Barker et al.), and the possibility of inducing a self-sustained rhythm has been previously discussed.\textsuperscript{1} If lateral propagation of impulses within the node is impossible during the relatively refractory period, as suggested above, then the circumstances which permit an echo response to occur should leave the two intranodal pathways out of phase and provide the opportunity for repetition of the event. That is, the echo response should engage the final common elements in the node, find the retrograde pathway previously taken by $H_2$ recovered, and return once more to the atrium. The necessary conditions for such a circuit would be: (1) the round-trip conduction time for $H_2$ (from the point at which dissociation occurs within the node, to the atrium, and back to that point) must exceed the refractory period of the retrograde conduction pathway; (2) lateral propagation must be impossible for the return impulse above the level of the dissociation, so that the retrograde pathway is not occluded by a short circuit; (3) an equilibrium must be reached at which the round-trip circuit time and the RP of the limiting components of the pathway remain in balance.

While the conditions necessary for self-sustained activity are theoretically possible, they appear to occur only rarely under the usual experimental conditions. There are a number of reasons why this should be so, but chief among them is the observed effect of frequency upon the position and dimensions of the echo zone. The round-trip conduction time, as measured by the $H_2H'$ interval, was...
of the order of 300 msec in most experiments when \( H_1H_2 \) was chosen to yield the minimal \( H_2H^1 \) interval. The actual round-trip from the point at which intra-nodal dissociation occurs must in general be less than this, in other words, the cycle length for a self-sustained repetitive tachycardia would have to be less than 300 msec. But, as we have seen (fig. 11), retrograde propagation becomes quite precarious at rapid frequencies; one must expect, therefore, that if and when the echo response re-enters the retrograde limb of the pathway, it will be likely to fail before reaching the atrium. Although the frequency could hypothetically be reduced by prolonging conduction time by vagal stimulation, the same agency merely shifts the whole pattern to the right and further depresses the retrograde pathway.

In the one case of experimentally induced self-sustained arrhythmia previously reported, the frequency was nearly 300 per min, a rate which could not have been sustained in the present experiments. It is obvious that the necessary conditions could only be achieved under the influence of an agency which facilitates intra-nodal propagation, particularly in the retrograde direction, and simultaneously abbreviates the effective RP of the limiting element in the pathway. Such an agency, of course, is epinephrine (fig. 11). It thus appears possible that with a properly chosen level of adrenergic activity, and at a properly chosen basic driving frequency, premature excitation of the His bundle (or the ventricle) could, not uncommonly, precipitate a self-sustained reciprocal rhythm.

**TWO PATHWAYS OR MULTIPLE PATHWAYS?**

Most of the experimental results discussed above can be explained by assuming a longitudinal dissociation of the A-V node causing the formation of two functional pathways, but they do not exclude the possibility that fractionation into more than two pathways may occur. Scher et al. have, in fact, suggested that the upper margin of the node may be broken down into multiple pathways; and Kistin has described clinical situations which he explains in terms of multiple pathways. Whether there are more than two does not alter the conclusions already reached. If a premature \( H_2 \) response is blocked at some junctional point within the node but continues to propagate through several collateral independent channels, it is evident that the time relations of the resulting events will be determined by the route which provides the shortest conduction time.

One might expect that, if several independent routes become dissociated, discontinuities in the curve relating \( H_2A_2 \) propagation time to the \( H_1H_2 \) interval should commonly occur; and, providing that \( H_2A_2 \) is sufficiently long, echoes should occur on either side of the break in the curve. In one experiment, of several in which a discontinuity occurred, the break was included in the echo zone. It is conceivable that at the longest effective \( H_1H_2 \) interval in this experiment (i.e., to the right of the break) the retrograde response reached the atrium over the faster of two (or more) pathways, but still slowly enough to permit a return impulse. Shorer \( H_1H_2 \) intervals, to the left of the break, propagation could have been accomplished over a route with a briefer RP but longer conduction time. The available data do not permit a firm conclusion in this experiment.

**VENTRICULAR ECHOES VS. ATRIAL ECHOES**

Longitudinal dissociation of the A-V node can be readily induced by premature stimulation of the ventricles or of the His bundle; previous studies indicate that dissociation can also be exposed by premature atrial stimulation. The clinical counterpart, termed "reversed reciprocal rhythm," has been described by Katz and Pick. There is, however, no evidence to indicate whether the intranodal scission is the same when induced from above or below; but when atrial echoes occur, it is clear that they must return over a pathway capable of retrograde propagation, i.e., not completely polarized in the orthodromic direction. This would suggest that the route traversed by early premature atrial responses is precisely that route which fails to transmit early premature His bundle responses in the reverse direction. It is of course possible that
dissociation occurs along a cleavage plane which is determined by the relative margins of safety along different pathways, and by the degree of prematurity of the triggering response, and that the plane is not, except perhaps by chance, the same in both directions.

Summary

Reciprocal responses (ventricular “echoes”) were initiated by premature stimuli applied directly to the bundle of His in dog hearts perfused from donor animals. The time relations of the responses in the His bundle and at the atrial margin of the exposed A-V node were studied under a number of conditions. It was found that:

1. The earliest premature response that can be induced in the His bundle is not propagated back to the atrium and does not lead to an echo.

2. There is, in most hearts, a continuous range of $H_1H_2$ intervals (the echo “zone”) within which reciprocal responses of the His bundle occur.

3. The earliest effective $H_2$ propagates slowly to the atrium, and the echo returns quickly.

4. The latest effective $H_2$ responses propagate more quickly to the atria, but return more slowly.

5. The atrium is an essential link in the echo pathway; i.e., the $H_2$ response must reach and activate the atrium before a return is possible.

6. Direct stimulation of the atrium in advance of the expected arrival of the $A_2$ response propagated from the His bundle can initiate a response which propagates to the bundle; i.e., two responses can travel in opposite directions on a collision course, yet one of them can complete its journey.

7. The limiting parameter of the return pathway is the refractory period of that portion of the lower node which must fire twice in the echo circuit.

8. The limiting element is not the bundle of His.

9. The limiting element can be discharged by early $H_2$ responses which fail to reach the atrium.

10. The refractory period of the limiting element is a function of the preceding cycle length.

It was also demonstrated that the echo “zone” is shifted to a range of longer $H_1H_2$ intervals when the basic driving frequency is increased, or when the vagi are stimulated. Epinephrine shifts the echo zone to a range of briefer $H_1H_2$ intervals.

It is suggested that echo responses occur when a retrograde impulse is arrested at one site within the node and continues to propagate to the atrium through collateral pathways. If the retrograde propagation time is long enough to permit the recovery of the lower elements of the node, an echo response reaches the His bundle. It was concluded that a self-sustained repetitive circuit may be possible when the round-trip conduction time exceeds the refractory period of the limiting tissue in the node.

References


VENTRICULAR ECHOES


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