Functional Properties of the Atrioventricular Conduction System

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The nature of the system responsible for transmission of excitation from atria to ventricles of the mammalian heart has been a recurrent problem in physiology. In 1910 Erlanger demonstrated conclusively that the only normal functional connection between these chambers is the specialized tissue of the bundle of His. However, anatomical evidence showing the occasional presence of other connections composed of muscular tissue has been provided by the studies of Kent, Lev, and Truex, among others. The syndrome described by Wolff et al. suggested that anomalous atrioventricular excitation might result from the spread of activity over pathways which were anatomically distinct from the atrioventricular node and bundle of His. Quite recently James demonstrated several tracts of fibers in human hearts which bypass the A-V node and which thus might establish functional A-V connections. In 1956 Moe made a detailed and exhaustive analysis of the spread of premature impulses from the atria to ventricles and in the opposite direction. On the basis of this analysis he postulated the existence of a dual A-V transmission system in which two groups of fibers differed with respect to duration of refractoriness and conduction velocity. Although gross anatomical duality was not implicit in his treatment, many subsequent investigators have reached the opposite conclusion. Rosenblueth independently arrived at conclusions similar to those of Moe on the basis of somewhat similar experiments. A number of workers (see Scherf; Katz and Pick) have assumed a "longitudinal functional dissociation" in some part of the A-V transmission system in order to account for certain disturbances of rhythm and conduction. This dissociation might result from functional impairment and resulting unidirectional propagation similar to that demonstrated by Schmitt and Erlanger.

We have been interested in exploring by electrophysiological techniques the entire range of function of each part of the A-V conducting system both in vitro and in vivo. Some of the results of these studies seem to bear on the question of whether or not a dual system is necessary to account for the observed variations in the pattern of A-V excitation. Although we have not made histological studies of the hearts employed in this work, the electrophysiological findings impose certain limits on any accessory anatomical pathways which might be operative in producing the observed changes in A-V transmission or in the pattern of ventricular excitation.

Methods

A. CANINE HEARTS IN SITU

1. Proportion of Animals

Adult mongrel dogs were anesthetized with intravenous thiopental sodium. Either during total cardiopulmonary bypass or during repeated inflow occlusion electrode plaques were attached, under direct vision, to the endocardium over the His bundle and over other selected parts of the specialized conducting system including the right
and left bundle branches and the peripheral Purkinje fiber-papillary muscle junctions. Similar electrodes were attached to the epicardial surface of the right atrium and the right and left ventricles. Each electrode plaque contained five silver wire contacts arranged in the form of an X. The diameter of the Teflon-coated wire was 0.4 mm and the distance between the contacts was 1.5 mm. The Teflon-coated wires were sheathed in polyethylene and led to the body surface. Adjacent pairs of contacts within an electrode plaque were used either for stimulation or for recording.

2. Acute and Chronic Experiments

A limited number of experiments were carried out acutely during maintained cardiopulmonary bypass. The majority of animals were allowed to recover from the surgical intervention and experiments were performed at intervals of one week to three months after electrode implantation. These chronic animals were lightly anesthetized with pentobarbital-Na (28 mg/kg iv) during each experiment.

During an experiment hearts were driven at selected rates through one pair of electrodes by means of rectangular pulses ($S_1$) supplied by an American Electronics stimulator and stimulus isolation unit. Pulse duration was 3 msec; stimulus strength was twice threshold. A second stimulator delivered test pulses ($S_2$) at selected intervals after the drive; these test pulses were isolated from ground and applied through adjacent pairs of electrode contacts to the atrium, ventricle, or selected parts of the specialized conducting system. Bipolar electrogams were recorded from each part of the heart along with one or more standard limb leads. These electrogams were displayed on an eight-trace switched-beam oscilloscope and photographed on paper moving at 200 mm/sec. Measurements of the record were made with the help of a mechanical device which provided an accuracy of ± 1 msec. Low frequency components of the electrogams were filtered to increase baseline stability and enhance recognition of complexes resulting from depolarization of specialized fibers. The effect of this procedure on the recording is demonstrated in figures 2 and 9.

Animals were studied repeatedly at intervals of days or weeks; reproducibility of results was quite satisfactory during single and repeated experiments.

B. ISOLATED PREPARATIONS OF CARDIAC TISSUE

Transmembrane resting and action potentials were recorded from isolated preparations of canine Purkinje fibers, papillary muscle, and ventricular muscle. Hearts were removed through a left lateral thoracotomy from dogs which had been anesthetized with pentobarbital-Na, 32 mg/kg iv. Purkinje fiber preparations consisted of part of the right bundle branch and its continuation in the free-running bundle of Purkinje fibers which extends from the base of the anterior papillary muscle to the endocardial surface of the free wall of the right ventricle. The tissues were immersed in flowing modified Tyrode solution maintained at 37°C and gassed with a mixture of 95% O$_2$-5% CO$_2$. Driving and testing pulses which were isolated from ground were applied through surface electrodes in a manner described previously. Transmembrane potentials from selected fibers were recorded through intracellular microelectrodes which were filled with 3 M KCl. Bioelectric Instrument preamplifiers and a switched-beam Teletronix oscilloscope were employed. Electrical resistance of the microelectrodes varied from 18 to 20 megohms. Voltage calibration was made by injecting a 100 mv signal between the bath and ground.

Results

In order to provide an orientation for the experimental results to be presented, a brief summary of several observed patterns of A-V excitation will be given. This summary is based largely on our understanding of the results of experiments conducted by Moe and his associates. If a test pulse ($S_2$) is applied to the atrium at shorter and shorter intervals after a rhythmically driving stimulus ($S_1$), the interval between the driven and premature ventricular responses may change in one of the ways shown in figure 1. In this graph the interval between the driven ($A_1$) and premature ($A_2$) atrial response is shown on the abscissa and the interval between the corresponding driven ($V_1$) and premature ($V_2$) ventricular responses on the ordinate. As the interval between $A_1$ and $A_2$ is decreased below a critical value, the interval between $V_1$ and $V_2$ either remains constant (curve 1), increases gradually (curve 2), or increases abruptly to a fairly constant value (curve 3). Associated with the abrupt increase in $V_1$-$V_2$ intervals of curve 3, and also at times with the gradual increase of curve 2, there may be a change in configuration of the QRS complex or ventricular electrogam. Also, reentrant beats or echoes are likely to appear. Similar changes have been observed for V-A transmission.

The increased $V_1$-$V_2$ intervals, the altered
sequence of excitation of the ventricles, and the re-entrant excitation are thought to come about in the following manner. When propagated activity initiated in the atria reaches the A-V transmission system too soon after the preceding impulse, components of the conducting system which conduct rapidly are still effectively refractory. However, excitation spreads to the ventricles over other components of the A-V system which conduct more slowly but which have a shorter effective refractory period. Because of the slower conduction, the $V_1$-$V_2$ intervals are increased. Because activity spreads over different components of the A-V conducting system, the morphology of the ventricular complex is changed. Re-entrant excitation takes place over the component of the dual system which has the longer refractory period; this results in echo beats.

In the following sections we have attempted to present our analysis of two of these phenomena based on direct recording from the specialized conducting system. Re-entrant excitation will be considered in a separate publication. Results are reported and analyzed under three headings: delay in the A-V nodal region, delay in the His-Purkinje system, and transmembrane potentials of single fibers.

A. DELAY IN THE A-V NODAL REGION

1. Type 1 Curves

When a plot of the transmission of premature atrial activity to the ventricles gives a curve of type 1, the delay appears to be localized to the region of the A-V node. This type

FIGURE 1

Diagram showing the three more common variations in the relationship between the interval separating driven ($A_1$) and premature ($A_2$) atrial impulses and the interval separating the resulting driven ($V_1$) and premature ($V_2$) ventricular responses. Curve 1, solid line; curve 2, dotted line; curve 3, interrupted line. See text for description.

FIGURE 2

Records obtained through chronically implanted electrodes showing characteristic bipolar electrograms from: RA—right atrium; BH—bundle of His; RPPJ—right Purkinje fiber-papillary muscle junction; RV—endocardial surface of right ventricle; II—standard lead II. A represents the atrial electrogram, H the His electrogram, S the complex resulting from depolarization of the base of the interventricular septum, P the Purkinje fiber electrogram, and M the complex recorded from the papillary muscle. The records shown in figure 2A are recorded with the standard time-constant and frequency response used in electrocardiography; for the direct bipolar electrograms in figure 2B the low frequency components of the trace have been filtered. It is apparent that the amplitude of the II and P complexes is increased relative to that of deflections due to activity in atrial and ventricular muscle. This procedure is followed in all subsequent figures. Time lines at intervals of 100 msec.
Chronic dog no. 2177. Relationship between the interval separating driven (A\(_1\)) and premature (A\(_2\)) atrial responses and the interval separating the resulting driven and premature responses recorded from the anterior papillary muscle of the right ventricle (M\(_1\)-M\(_2\)) and from the bundle of His (H\(_1\)-H\(_2\)). The solid line is the theoretical line of no A-V conduction delay. Since, for each value of A\(_1\)-A\(_2\), the values of H\(_1\)-H\(_2\) are the same as M\(_1\)-M\(_2\), there is no delay distal to the recording electrode on the bundle of His. Basic cycle length is 350 msec.

Data obtained from a chronic preparation which gave a type 1 curve are shown in figure 3. The plot of A\(_1\)-A\(_2\) intervals against M\(_1\)-M\(_2\) intervals is quite similar to the schematic curve of type 1 in figure 1. M\(_1\) and M\(_2\) represent the responses recorded from the anterior papillary muscle of the right ventricle. Since for each premature atrial response the intervals between the driven (H\(_1\)) and premature (H\(_2\)) responses of the bundle of His are the same as the intervals between M\(_1\) and M\(_2\), conduction from the His bundle to the ventricles proceeds at normal velocity at all A\(_1\)-A\(_2\) intervals and the delay in A-V transmission is localized to the region of the A-V node. Although not shown in figure 3, if the V\(_1\)-V\(_2\) intervals, representing the time of activation of the epicardial surface of the right ventricle, are employed, the curve has the same shape as that shown for M\(_1\)-M\(_2\) intervals. Since atrial activity is recorded close to the A-V node, possible slowing of conduction of premature atrial responses is of little importance. In this sort of experiment the electro-
Bipolar electrograms recorded from the right atrium (RA), bundle of His (BH), right Purkinje fiber-papillary muscle junction (RPPJ), and the epicardial surfaces of the right (RV) and left (LV) ventricles of dog no. 2182. Also shown is lead II of the standard electrocardiogram. Time lines at intervals of 40 msec. The His electrogram shows three complexes: the first (A) represents local atrial activity; the second (H), activity in the His bundle; and the third, depolarization of the base of the interventricular septum. In the record from the RPPJ the first complex (P) is due to activity of the Purkinje fibers and the second (M) is due to activity of the papillary muscle. The arrow (S) shows the time of application of the test stimulus. The approximate time required for nodal transmission of a driven atrial response (A) and a premature atrial response (A) is shown by the length of the lines of 1 and 2.

gram complexes recorded from His bundle, peripheral Purkinje fibers and ventricle, and the QRS complex of the ECG show no changes in amplitude or configuration during propagation of premature atrial responses.

These results show that a curve of type 1 is obtained when the delay in conduction between the atria and bundle of His increases in direct proportion to the prematurity of the propagated atrial response which reaches the A-V nodal region. The point of inflection of the curve presumably defines the end of the effective refractory period of the A-V node. Since this is the longest effective refractory period between atria and ventricles in this experiment, conduction in and distal to the His bundle is normal.

2. Type 2 Curves

Curves of the type 2 configuration also usually result from a delay in the transmission of excitation from the atrium to the bundle of His. This type of curve was obtained from the majority of chronic preparations. Results from one experiment of this sort are shown in figures 4 and 5. The tracings in figure 4 show bipolar electrograms recorded from the atrium, the bundle of His, the Purkinje fibers at the right anterior Purkinje-papillary muscle junction, and the epicardial surface of the right and left ventricles. The delay in transmission of an early atrial extrasystole at the A-V node is evident from the increased interval between A and H. The results obtained in this experiment differ from those described above for the type 1 curve in one primary respect: the increment in delay of transmission in the A-V nodal region increases progressively as the premature atrial response arrives earlier and earlier in the cardiac cycle. This is shown in...
FIGURE 5A
Relationship between the interval separating driven (A₁) and premature (A₂) atrial responses and corresponding responses of the His bundle (H₁, H₂) and the right anterior papillary muscle (M₁, M₂). The solid line indicates the theoretical relationship in the absence of any increment in delay of transmission.

FIGURE 5B
The responses shown for short A₁-A₂ intervals in "A" are plotted as the relationship between H₁-H₂ and M₁-M₂. Also shown is the interval between driven (P₁) and premature (P₂) responses of the Purkinje fibers at the RPP. The slope of the interrupted line shows no change in conduction time from H to P or M.

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As the interval between the driven (A₁) and premature (A₂) atrial responses is reduced, the intervals between corresponding driven (H₁) and premature (H₂) responses of the His bundle decrease to a minimum and then increase progressively. The intervals between driven (M₁) and premature (M₂) responses of the anterior papillary muscle of the right ventricle follow the same course.

In figure 5B the intervals between the driven and premature responses of the His bundle (H₁ and H₂) are plotted against the interval between M₁ and M₂. Also shown are the intervals between driven (P₁) and premature (P₂) responses of peripheral Purkinje fibers at the right Purkinje fiber-papillary muscle junction. The data are closely distributed around the line indicating no conduction delay. Conduction from the His bundle to peripheral Purkinje fibers and ventricular muscle thus proceeds at normal velocity for all atrial responses and delay is confined to the region of the A-V node. As far as one can judge from the ventricular electrograms and electrocardiogram (fig. 4), the pathway over which ventricular excitation takes place is the same for driven and premature responses. The probable mechanisms for the two types of nodal delay which give rise to type 1 and type 2 curves is discussed below. The possibility of delay at more than one site also is considered.

8. Delay in the His-Purkinje System

It has been shown that the duration of the transmembrane action potential increases from the His bundle to the peripheral Purkinje fibers. Also, under certain conditions a premature atrial response may spread through the A-V node and excite the fibers of the His bundle before these fibers have completely repolarized. It is to be expected, therefore, that delay in A-V transmission of premature atrial activity might be localized in part or in toto to the His bundle, the bundle branches, or the more peripheral Purkinje fibers. This delay in the specialized conducting system distal to the A-V node has been found in two types of experiments:

When premature stimuli were delivered to the atria of acute preparations and when premature stimuli were delivered directly to the His bundle of chronic preparations. In these experiments it has been found essential to record directly from either the bundle branches, the peripheral Purkinje fiber-papillary muscle junctions, or both in order to obtain a more exact localization of the site of maximum delay in A-V transmission.

1. Atrial Stimulation

In a number of acute experiments premature atrial responses elicited quite early in the cardiac cycle spread through the A-V node to the His bundle with only a minimal increase in nodal transmission time. Records from two such experiments are shown in figures 6 and 7 because each demonstrates different aspects of the delay in activation of the ventricular conduction system and ventricles. In the experiment shown in figure 6, electrodes were attached to the endocardial surface of the right atrium over the His bundle, over both right and left bundle branches, and to the epicardial surface of the right ventricle. Lead II of the electrocardiogram also was recorded. Test stimuli were delivered to the atrium through two of the contacts in the His electrode. Late in the cycle premature atrial responses spread through the A-V node and to the ventricles without delay (fig. 6A) and the configuration of the ventricular premature response in lead II is the same as that of the driven responses. Earlier atrial premature beats are delayed only slightly in the node as is shown by the timing of the H complex in relation to the stimulus artifact. These responses are delayed slightly in reaching both the right and left bundle branches (fig. 6B). The electrograms recorded from the right and left bundle branches are decreased in amplitude and slurred or notched. The electrocardiogram shows a moderate alteration in the configuration of the QRS complex. Following a still more premature atrial response (fig. 6C), the changes just mentioned become more marked; there is delay in conduction from the bundle branches to the ventricle and both the local...
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Records obtained during an acute experiment from the bundle of His (HH), left (LB) and right (RB) bundle branches, and right ventricle (RV).

The bottom trace is standard lead II; the second trace from the bottom shows the time of application of the $S_2$ stimulus to the atrium through one pair of contacts in the His electrode. $A$, $B$, and $C$ show responses to stimuli applied progressively earlier in the cardiac cycle. $S_2$ causes a large artifact in the BH record. Time lines at intervals of 40 msec. The fact that the $S_2$ current stimulates the atrium is apparent from the $S_2$-H interval and the sequence of activation of the specialized conducting system and ventricles. Note the relatively short $S_2$-H interval throughout, the change in configuration and amplitude of the LH and RH complexes following early activation of the His bundle, and the altered sequence of activation of the ventricles in $B$ and $C$. The response to the $S_2$ stimulus which follows $S_2$ in $C$ also shows disturbances of conduction in the specialized tissues. See text for discussion.

In the experiment shown in figure 7 electrograms were recorded from the atrium, His bundle, right and left bundle branches, and Purkinje fiber-papillary muscle junction. In figure 7 the tracings from the right bundle branch and right Purkinje-papillary junction are shown. The similarity of delay in both ventricles is shown in figures 8A and 8B. A premature atrial response ($A_2$) shown in figure 7A is delayed only slightly in the A-V node. Activity propagates from His bundle ($H_2$) to right bundle branch before the latter is fully recovered; this is shown by the change in the local electrogram ($B_2$). An earlier atrial response (fig. 7B) again traverses the A-V node with only moderate delay and reaches the His bundle before local recovery is complete. This is shown by the changes in the $H_2$ complex.
Spread of activity from the His bundle to the ventricles is markedly altered. A very low-voltage complex (B₂) is recorded from the right bundle branch and there is no evidence of any electrical activity in the Purkinje fibers at the right Purkinje-papillary junction. The electrogram recorded from the papillary muscle (M₂) is changed in configuration and markedly delayed; the sequence of activation of the ventricles also is changed as can be seen from the electrograms recorded at each site. Somewhat similar alterations are shown for the succeeding driven beat.

The timing of electrograms recorded from the bundle of His, right bundle branch, and right Purkinje-papillary junction in response to premature atrial stimuli applied at a number of different intervals of the cardiac cycle is shown in figure 8A. It is clear that, if the time of activation of the ventricles is judged on the basis of the electrogram complex recorded from the anterior papillary muscle of the right ventricle, the curve relating A₁-A₂ to M₁-M₂ is of type 3 (fig. 1). The interrupted line in this figure shows no increment in A-V delay; it is apparent that delay proximal to the His bundle is minimal for all values of A₁-A₂. The major part of the increment in the M₁-M₂ interval, as well as the aberrant pattern of ventricular
excitation, results from altered excitability and conduction in peripheral Purkinje fibers, presumably due to local prolongation of the duration of the effective refractory period. The absence of P2 complexes at short A1-A2 intervals may indicate complete failure of excitation of these Purkinje fibers. It is possible, however, that because of extremely slow conduction the close bipolar electrograms failed to indicate the presence of activity.

Many observations suggest that conduction disturbances are more likely in the right than the left bundle branch. In order to emphasize the fact that the delays of the type just shown are present in both right and left sides of the specialized conducting system, data obtained in the same animal from the left bundle branch and left Purkinje-papillary junction are shown in figure SB. Although there are quantitative differences from the data shown in figure SA, it is apparent that an abrupt increment in A-V delay is localized to the Purkinje system distal to the bundle of His.

The data shown in figures SA and SB also demonstrate the fact that delay in propagation of premature atrial activity to the ventricles may occur at more than one location in the specialized conducting system. In figure SA, at short A1-A2 intervals, it is evident that there is some delay of transmission between the atrium and the bundle of His.
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This is shown by the divergence of the His bundle points from the line of no delay. A slight delay between the His bundle and bundle branch also is apparent. In figure 8B there is once more some delay of propagation from atrium to His bundle at short A1-A2 intervals. In addition, there is a marked delay between activation of the HNS and the peripheral Purkinje fibers and, at certain intervals, some delay either between Purkinje fibers and muscle or between His bundle and bundle branch. It is interesting to note that the delay between Purkinje fibers and muscle decreases as activation of the Purkinje fibers takes place later in the cycle. One other observation should be emphasized. If we consider only the responses recorded from the papillary muscles of the right and left ventricles, the curve in figure 8A is of type 3 while that in figure 8B is of type 1.

A number of chronic animals were tested in an attempt to produce, under these conditions, the same pattern of atrioventricular transmission shown in figures 6, 7, and 8; in each instance the premature atrial stimuli were delayed sufficiently in reaching the His bundle so that more distal parts of the conducting system had recovered almost completely from previous excitation. It was thought that the atrioventricular delay of premature atrial impulses in these animals might be altered in such a way that a curve of type 2 would be changed to type 3. To accomplish this, the following experiments were performed. In some animals ouabain was infused intravenously until toxicity was indicated by the appearance of multiple ventricular extrasystoles. In other animals epinephrine or norepinephrine was infused at a rate just insufficient to cause ventricular extrasystoles. Also the frequency of S1 stimulation was varied over the maximum possible range. Although each of these procedures caused the expected changes in A-V transmission of the driven atrial responses and although there was some change in the configuration and inflection point of the curve relating A1-A2 to V1-V2 intervals, it was not possible to obtain a curve of type 3.

2. Stimulation of the His Bundle

Although it was reasonably certain that our inability to produce a curve of the type 3 configuration in chronic animals during atrial stimulation resulted from the failure of propagated activity to reach the His bundle with sufficient prematurity, some additional experiments were conducted. In these, premature stimuli were delivered directly to the bundle of His through chronically implanted electrodes. The object of these tests was to determine whether or not the results obtained in acute experiments were in any way influenced by the experimental technique or the condition of the heart. In particular, we wished to learn if premature activity in the His bundle would be delayed in propagation to the ventricles and if the sites of delay and patterns of excitation would be the same in chronic animals as had been shown under acute conditions.

Since the electrode used to record from, and stimulate, the bundle of His was in contact with the overlying atrial muscle, the atrium always was excited by stimuli of an intensity sufficient to attain threshold for the His bundle. Also, an electrode in this position is in close proximity to the base of the interventricular septum and strong stimuli thus may cause direct excitation of this tissue. Although the complex strength-interval curves which may result under these conditions have been described and discussed elsewhere, the records in figure 9 are presented to give a brief summary of the criteria employed to identify direct stimulation of the His bundle. It is quite obvious from the resulting changes in sequence of excitation of the heart when the test stimuli excite the ventricle directly. The presence of a normal or prolonged interval between the atrial and His electrogram indicates that the premature stimulus has excited the atrium but has failed to excite the His bundle directly. Although there may be a considerable local "latency" when stimuli are delivered directly to the His bundle early in the refractory period, in our experience this latency has not been so long as to be mistaken for A-V nodal delay.
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The data obtained from one experiment of the type just described are presented (fig. 10) to indicate the response of the specialized conducting system of chronic animals to premature activation of the bundle of His. Responses at two recording sites in the ventricle are included in this graph—the right Purkinje fiber-papillary muscle junction and the epicardial surface of the right ventricle. In this figure the abscissa shows the time of stimulation of the His bundle rather than the time of the local His electrogram. This was done because stimulus artifact and local atrial activity obscured the H complex (fig. 9C). On the ordinate are shown the intervals between driven (Vi) and premature (V2) responses recorded from the right ventricle and driven and premature responses from the Purkinje fibers (P1, P2). As the H1-H2 interval was decreased there was a similar change in RV1-RV2, P1-P2, and M1-M2 intervals until the H1-H2 interval was less than 175 msec. With further decreases in H1-H2, the interval between the responses at the peripheral recording sites remained constant for several stimuli and then, at the shortest H1-H2 intervals, increased abruptly. It should be noted that the increment in P1-P2 is about 25 msec greater than that in V1-V2. This shows two points of interest. First, a large part of the delay causing the increment in P1-P2 must have been localized to the peripheral Purkinje fibers. Second, the magnitude of the conduction delay differs in different parts of the Purkinje system. This latter fact also is shown by a comparison of figures 8A and 8B. The change in configuration of the QRS complex at short H1-H2 intervals, which resulted from premature stimulation, is shown in figure 11.

The responses of the anterior papillary muscle are not plotted in figure 10 because to do so might give the erroneous impression that the papillary muscle was excited before the adjacent Purkinje fibers. This is a limitation of the type of presentation used to construct the curves. Since the increment in delay between P1 and P2 is greater than the increment in delay between M1 and M2, the M1-M2 intervals would fall below the P1-P2 intervals on the graph. Inspection of figure 11 shows, however, that the M2 responses did indeed follow the P2 responses as would be expected.

One other aspect of figure 10 should be emphasized: the responses to the two earliest stimuli which excited the His bundle gave relatively short P1-P2 and V1-V2 intervals. This finding was not a frequent occurrence; it has been noted by others and will be discussed below. It should be stated, however, that we do not believe the observation just mentioned indicates the existence of a period of "supernormal" conduction in the usual sense of the term.

The data obtained from direct stimulation of the His bundle of chronic animals confirmed the possibility that, under these conditions, premature activation of the bundle of His would cause delays in activation of peripheral Purkinje fibers and an altered sequence of activation of the ventricles.

C. TRANSMEMBRANE POTENTIALS OF SINGLE FIBERS

The records obtained directly from various parts of the specialized conducting system of the in situ canine heart show that responses to premature atrial stimulation may be delayed in the region of the A-V node or may propagate relatively rapidly through the node only to be delayed in the His bundle, the bundle branches, or the peripheral Purkinje fibers. Associated with premature activation of the fibers of the His bundle there is evidence of slow conduction or block in more peripheral parts of the His-Purkinje system and an abnormal sequence of activation of the ventricles. Presumably these changes are a result of activation of fibers which have not completely recovered from previous activity and thus, at least in the His-Purkinje system, are not fully repolarized. The relationship between the response of Purkinje fibers and the level of membrane potential at the time of stimulation has been clearly demonstrated. Also, the response of fibers in different parts of the A-V node to premature activation has been described.
Records from chronic dog no. 1517 showing the complexes which result from application of driving stimuli \( S_1 \) to the bundle of His. RA—right atrium, BH—bundle of His, RPPJ—right Purkinje fiber-papillary muscle junction, RV—right ventricle, II—standard lead II. In A there is a normal sinus rhythm and the bipolar electrograms are unfiltered. In B the electrograms are filtered in the usual manner and \( S_1 \) is applied to the right atrial appendage. In C, \( S_1 \) is applied to the His bundle through one pair of contacts in the RV electrode. The stimulus causes a marked artifact in the RV trace, obscuring the II complex completely, and in lead II (arrows). The normal activation of the specialized conducting system and ventricles is apparent from the \( S_1-P \) interval, from the timing and configuration of the RPPJ and RV electrograms, and from lead II. Time lines at intervals of 100 msec.

At this time we will present results obtained from a limited number of experiments on isolated preparations in an effort to demonstrate the essential characteristics of responses to premature activation. Subsequently, we will attempt to correlate the transmembrane potentials recorded from single fibers and the patterns of response recorded from the intact, in situ heart.

It has been shown that the duration of the transmembrane action potential increases from the bundle of His to the peripheral Purkinje fibers. This can be seen in figure 12 in the records of transmembrane action potentials of single Purkinje fibers located at the base of the anterior papillary muscle and in the free-running bundle which extends to endocardial surface of the free right ventricular wall. There is a greater difference in duration of action potentials recorded from the single fibers of the right bundle branch and from more peripheral Purkinje fibers (fig. 13). The transmembrane action potentials on the upper trace in figure 12 show that premature activation of this fiber results in a progressive decrease in the amplitude and rate of rise of the response until only a local, graded response is obtained. Comparison of the records on the upper and lower traces shows that these premature responses decrease in amplitude and rate of rise as they encounter tissue which is less fully repolarized and that, over a relatively short distance, decrement along this path may be complete. Complete decrement also is shown in figure 13A. This seems to us to be a clear demonstration that a premature response in the Purkinje system may be propagated at reduced velocity or may fail to propagate because of local differences in the duration of the transmembrane action potential. These changes may occur at any point between the His bundle and the peripheral Purkinje fibers during atrioventricular propagation.

The changes in the action potential shown
in figure 12 result in a gradual and progressive change in the spread of activity. This is not always the case. There may be, at times, a discontinuous increment in the delay in propagation of premature activity. This is shown in figure 13. The preparation included a segment of the right bundle branch (RBB) in addition to the anterior papillary muscle and the Purkinje fibers which run free in the ventricular cavity from the papillary muscle to the free ventricular wall. For the sake of brevity this bundle of Purkinje fibers is referred to by the term false tendon (FT). The first set of action potentials in figure 13A shows that repolarization of the fibers in the RBB precedes that of fibers in the FT; also, action potential duration in the FT increases as one approaches the periphery. The premature responses recorded from a fiber in the RBB show that all S2 stimuli resulted in action potentials which propagated from the papillary muscle to the Purkinje fibers at the Purkinje fiber-papillary muscle junction. The responses of the fibers in the RBB to these premature stimuli show the usual changes in amplitude and rate of rise as a function of the level of the membrane potential. In figure 13B and C the responses recorded from fibers in the FT show similar changes. However, somewhat earlier activation causes, at the proximal recording site in the FT, a response which arises from a step or prepotential (fig. 13D) Activation at a lower level of membrane potential increases the duration of this step (fig. 13E). Because of the local delay at the proximal recording site, the response recorded at the distal site in the FT shows a smooth and reasonably rapid rising phase (fig. 13D and E).

The relationship between the S1-S2 interval
Records from dog no. 1517 showing the aberrant ventricular response to early stimulation of the His bundle. Conventions are the same as in figure 9. In A $S_2$ falls relatively late in the cycle, activation of the specialized conducting system and ventricles is normal, and the only change in lead II is in the timing of the P wave relative to the QRS. This results because $S_2$ necessarily activates atrium at the same time as His bundle. In B the response to an earlier $S_2$ is delayed in its arrival at the RPPJ, the local electrograms are altered, and the QRS complex is grossly distorted. There is also a coupled response to $S_1$. In C the strength of $S_2$ was unchanged; however, it fell still earlier in the cycle and only the atrium was nonrefractory. This observation, coupled with the fact that the arrival of $S_2$ preceded the T-wave peak in lead II, shows that there was no direct stimulation of ventricular muscle in figure 11B.

and the time of the response recorded from the RVP and the distal site in the FT are plotted in the usual manner in figure 14. It is clear that, when the action potential upstroke is preceded by a prepotential or step, there is an abrupt increase in the $P_1-P_2$ intervals. The responses plotted for the RVP show that there is no other cause for this abrupt increase in delay in the preparation under study. The curve for the distal elec-
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Records of transmembrane action potentials recorded from an isolated preparation of right bundle branch, anterior papillary muscle, and peripheral Purkinje fibers. The insert shows the preparation and the arrangement of stimulating and recording electrodes. RB—right bundle branch, PM—papillary muscle, FT—false tendon extending to the right ventricular free wall. The bottom trace is recorded through the electrode in the FT, the middle trace through the distal, and the upper trace through the proximal electrode in the false tendon. S1 and S2 are applied to the papillary muscle. Time and voltage calibrations show 100 msec and 100 mv, respectively. Note, in A, that the duration of the transmembrane action potential is least for the RB and increases with distance in the FT. The responses to S2 applied progressively earlier after S1 are shown in A to E; see text for discussion.

Discussion

The results of this work are best divided into several categories for the purposes of discussion. The first has to do with any anatomical implications of these studies of electrical activity, the second with the probable mechanisms, in terms of transmembrane potential, responsible for conduction delay and block, and the third with the degree to which our observations may be representative of the normal behavior of the heart.

A. ANATOMICAL IMPLICATIONS

It should be stated at the outset that our results do not in any sense exclude the existence of accessory communications between the atria and ventricles of the canine heart. What we have tried to demonstrate is the range of response patterns which may result from premature activation of the specialized conducting system (SCS). In the experiments performed on intact animals we have recorded directly only from several selected parts of the SCS. It is obvious that we have not directly observed activity in many other parts of the same system in any given experiment; moreover, the possibility exists that we have not recorded at all from some other atrioventricular communication. The point to be emphasized, however, is the following. Regardless of the site of maximum delay of A-V transmission and regardless of the sequence of activation of the ventricles, we have recorded electrical activity during the spread of premature impulses through the same elec-
trodes used to record the normal sequence of A-V transmission. Moreover, with the exception of the most peripheral Purkinje fibers in a few experiments, activity always has been recorded from the His bundle, the bundle branches, and the Purkinje fibers during normal and premature activation and these records have always shown a regular, though delayed, sequence of activation. Several observations suggest that there have not been two groups of dissimilar fibers in the parts of the conducting system studied. The increase in duration of the local bipolar electrogram has not been great even with the most premature activation. Also, within a given cardiac cycle we have not observed any evidence of re-entrant excitation of any part of the His bundle or Purkinje system which might be expected to result from two parallel groups of fibers with effective refractory periods of quite different durations.

The sites of maximum delay in A-V transmission of premature atrial activity also have some bearing on the question of whether or not there are two anatomically discrete groups of fibers arranged in parallel. In many experiments a progressive increase in A-V delay (type 2) was clearly localized to the region of the A-V node. In these instances it could be shown directly by the local bipolar electrograms that excitation of the ventricles spread over the usual paths and in the normal sequence. In some animals a discontinuous increase in A-V delay (type 3) was observed. This appeared to result primarily from slow conduction or block in the peripheral Purkinje fibers. It was this sort of delay which was associated with an abnormal sequence of activation of the ventricular muscle. The type 3 curve and the altered sequence of ventricular excitation resulted both from stimulation of the right atrium and from direct stimulation of the bundle of His. This pattern of excitation thus did not necessarily depend in any way on the functional or anatomical properties of the A-V node. These experiments would appear to eliminate the necessary participation of any accessory or dual pathways above the level of the His bundle in production of the type 3 curve or the associated aberrant ventricular activation. Although we have not observed a type 3 curve when delay was localized to the node, such a happening may well be possible. However, it seems most unlikely that a marked change in the sequence of activation of the ventricles would result solely from a nodal mechanism and would require other associated changes in the activity of distal parts of the conducting system.

In all of our chronic studies we were limited to records from the His bundle and right side of the specialized conducting system. This was so because, at the time of these experiments, it was not practical to prepare chronic animals with electrodes implanted within the left ventricular cavity. However, in acute experiments it was demonstrated that, on early activation of the His bundle, delay of premature activity was present both in the right and left bundle branches. This is emphasized because of the general impression obtained from experiment and clinical observation that the right bundle branch is more prone to block than the left. The experiments reported here indicate that differences between the two bundle branches are quantitative and not qualitative.

8. PROBABLE MECHANISMS

There is a good deal of evidence which suggests that the changes in spread of activity from atria to ventricles observed in these experiments can be explained in terms of the level of membrane potential of the individual fibers and the demonstrated relationships between this value and the response of the fiber to stimulation. The tracings in figure 15 are provided to summarize the essential observations and to serve as a framework for this part of the discussion. Although, as has been indicated in the section on experimental results, there may be delay of a single impulse at several sites in series and although more than one type of delay may be operative during the transmission of a single impulse from the atria to ventricles, for the sake of ease of description two somewhat discrete mechanisms will be described separately.

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The diagrams in figure 15A and B show the change in rate of rise and amplitude of action potentials elicited when either the A-V node or Purkinje fibers are activated prior to complete recovery. In the case of the Purkinje fiber, it has been shown previously that it is the level of membrane potential prior to stimulation which determines the maximum rate of rise and amplitude of the response. For the A-V node this relationship is not so clear. Nevertheless, premature activation results in an action potential which spreads less rapidly than normal because of the reduced rising velocity and amplitude. The curve relating the level of membrane potential to maximum rate of rise is S-shaped and the voltage-time course of repolarization differs in different fibers. The relationship between prematurity of stimulation and local conduction velocity thus is not a simple one. Nevertheless, the more premature the stimulus the lower the maximum rate of rise and amplitude of the response and the slower the local conduction. If local delay due to the changes just described is sufficiently great, fibers in advance of the wave of propagation may recover completely. In this instance the conduction velocity will return to normal and propagation will proceed without interruption.

Under different conditions, which cannot be specified completely at this time, the delay of propagation may be somewhat different. When records are obtained from a single fiber at the junction between A-V node and His bundle (i.e., the NH region), the response to premature activation of the atrium is seen to rise from a step or prepotential (fig. 15C). The transition from a smooth, slow action potential upstroke to a prepotential may be gradual or quite abrupt. It is quite certain that this sort of prepotential results from marked decrement in the middle (N) region of the node. If the magnitude of the prepotential is such that membrane potential approaches the threshold potential slowly, there may be considerable local delay. Also, since the rate of change of membrane potential at the peak of the prepotential is very low, there may be a marked increase in local delay when the prematurity of the stimulus is increased only slightly. This local mechanism is thought to be responsible for the type 2 curve. Because of local delay in the node, distal fibers recover completely and conduction in His bundle and Purkinje fibers is normal.

The same sort of local mechanism may cause delay anywhere in the His-Purkinje system (fig. 13). The major difference is that, in this situation, the appearance of a step-like prepotential results from a local increase in action potential duration in the path of the premature propagated response. Usually this condition is encountered in the more peripheral Purkinje fibers. As the prematurity of the stimulus is increased the transition from a smooth, slowly rising action potential of reduced amplitude to a response which arises from a prepotential or step often is abrupt (fig. 13). This produces the type 3 curve (fig. 14). As is shown in figure 13, the local delay which arises in this manner permits more complete recovery of distal fibers and a restoration of more normal conduction. If the magnitude of local delay is
sufficient, or if some Purkinje fibers fail completely to conduct, the pattern of activation of the ventricles will be changed. The A-V node and Purkinje fibers differ in their response to premature activation in only one primary respect: in the Purkinje fibers, premature responses are altered in relation to the level of membrane potential. Action potential duration thus is of major importance. In the N region of the A-V node, however, premature responses may show increased decrement even after the full membrane potential has been restored. The reasons for this difference require further study.

We have not made any study of re-entrant excitation or "echoes" because the hearts used in this study were driven at a regular and rapid rate and because the driving stimulus ($S_1$) immediately following $S_2$ was not dropped. It has been shown that, in an animal exhibiting a type 3 curve, the abrupt increase of the $V_1$-$V_2$ intervals is associated with an absence of evidence of local electrical activity in some parts of the peripheral Purkinje system. If these Purkinje fibers are indeed not excited during A-V propagation they might be available for re-entrant activation. In our experiments the proper time sequence for this event was not present. Nevertheless, the mechanism, if operative, would not differ markedly from that postulated by Moe. It is possible also that in some nodal fibers decrement in transmission of premature atrial activity is complete. Such fibers might be excited after a considerable lapse of time by activity originating late during a step-like prepotential. Again, although the mechanism seems possible, we do not have direct evidence from the present studies.

One additional observation deserves some mention. During an experiment which resulted in either a type 2 or type 3 curve, there often was considerable scatter of the $V_1$-$V_2$ intervals at short $A_1$-$A_2$ intervals. Also (fig. 10) at times the shortest $A_1$-$A_2$ intervals resulted in rather short $V_1$-$V_2$ intervals so that the points plotted for the latter fell in the position appropriate for a type 1 curve. This phenomenon may be termed supernormal conduction by analogy to certain clinical observations. The implication of the finding, however, is quite different from that usually expressed. Impulses which enter the His bundle soon after previous activity may spread at near normal velocity through the bundle branches and encounter partially depolarized membrane only in the periphery. This results in the local delay shown in figure 13. An impulse which is initiated slightly earlier in the cycle may encounter partially depolarized tissue in the His bundle or bundle branches. Because the local differences in action potential duration are slight, propagation is slowed but there is no significant local delay. This impulse thus reaches the ventricle earlier than one initiated slightly later in the cycle. The extreme case has been described by Moe, in which propagation failed completely at rather short $A_1$-$A_2$ intervals only to succeed if the prematurity of $A_2$ was increased. The same phenomenon has been recorded in studies of isolated canine false tendons. The individual points in figures 8A and 8B show several examples of this relationship between proximal slowing of conduction and distal delay. The term supernormality seems most inappropriate for this variation in conduction since it implies a conductivity greater than normal.

C. IMPLICATIONS REGARDING NORMAL CARDIAC FUNCTION

There are only two points to mention in relation to any possible extension of these results to an understanding of the function of the normal heart. The first question which might be raised concerns the use of isolated preparations of cardiac tissue to study electrophysiological behavior. Most of the observations on premature activation of Purkinje fibers and A-V nodal fibers were completed before it was possible to record directly from the in situ conducting system. The experiments on chronic animals were made in part to evaluate the data obtained from isolated tissues. The similarity between the phenomena recorded from isolated tissues through microelectrodes and those from intact animals through chronically implanted elec-
trodes suggests to us that use of the former preparation was permissible. The second major question is the extent to which the normal function of the in situ specialized conducting system has been influenced by the experimental intervention. The results of acute experiments conducted during total cardiopulmonary bypass differ from those obtained from lightly anesthetized chronic animals only in regard to the presence of the type 1 curve in the former group. This was the curve seen by Krayser in 7 of 20 experiments on heart-lung preparations; thus it may indicate some unusual condition of the A-V conduction system. It is not likely that the appearance of either the type 2 or type 3 curve in chronic animals depends on the presence of electrodes on parts of the specialized conducting system since the same curves are obtained when electrodes are placed only on the atria and ventricles.

The data obtained from chronic animals thus may give an accurate picture of certain aspects of the range of function of the normal atrioventricular conduction system.

Summary

Experiments were designed to study A-V transmission of premature atrial responses by recording electrical activity directly from selected parts of the conducting system. This experimental design permits a more exact interpretation of results than is the case when records are obtained only from the atria and ventricles. The data obtained from chronic animals thus may give an accurate picture of certain aspects of the range of function of the normal atrioventricular conduction system.

Two types of experiments have been conducted in studies of the response of the specialized conducting system of the mammalian heart to premature activation. Records of transmembrane potentials from single fibers of the A-V node and Purkinje system show that premature responses may show a reduced rate of rise and amplitude and thus may be conducted slowly or may decrement completely. Under other conditions, premature responses may show local delay or block because they arise from a local response of considerable duration.

Records obtained directly from different parts of the in situ specialized conducting system show that the same phenomena probably occur in the intact, normal heart. These properties of the various fibers of the conducting system, in conjunction with the normal local differences in action potential duration, conduction velocity, and excitability, seem to account quite adequately for the variations which have been noted during A-V propagation of premature responses. On the basis of these results, it seems unnecessary to postulate a dual A-V conducting system in the mammalian heart.

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