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Studies on the Activation Process of Experimental Ventricular Extrasystole

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INTRODUCTION

Much interest was stimulated in electrocardiographers by ventricular extrasystole, because of its highest frequency amongst all the arrhythmias¹⁾²⁾ and its peculiar QRS complex configuration. The activation process in ventricular extrasystole, therefore, has been studied in very earliest stage of electrocardiography.

In 1887, Marchand³⁾ with the toad heart, and in 1910, Kraus and Nicolai⁴⁾ with the canine heart, produced artificial extrasystole and studied its ventricular activation process. Later, Lewis⁵⁾ and other investigators performed a number of experiments using the canine heart and there were some reports on experimentally produced extrasystole in the human heart^{6)–8)}. In all of these experiments, however, the stimulating foci and lead points were restricted to the epicardial surface. Furthermore, the method of producing and means of interpreting these experimentally produced extrasystole, theoretically, have not been adequate; thus, the process of ventricular excitation in extrasystole has not been definitely elucidated.

Recent progress in the research on intramural lead electrocardiograms has established a good deal of systematic knowledge of the normal activation process in the canine heart. In contrast, however, very few experiments on extrasystole in the ventricles are found in the literature by such investigators as Durrer^{9)–11)}, Scher¹²⁾¹³⁾, and Toyoshima¹⁴⁾¹⁵⁾ and their associates.

Elucidation of the activation process in ventricular extrasystole in conjunction with that of

normal activations may provide an important connection between the theoretical explanations of electrocardiographic deflections, and the relationship between the electrophysiology and the anatomy of the heart.

The activation processes in experimentally produced ventricular extrasystole in the ventricular free walls and the interventricular septum of the canine heart were investigated by using the technique of "minor ECG". The electrodes and stimulating unit employed in this study were especially devised for these experiments.

METHOD

1. Materials and technique

Fifty adult mongrel dogs weighing 8 to 16 kilograms were used in this series of experiments. Each dog was anesthetized with 30 milligrams of Oltopan Sodium per kilogram of body weight, which was administered intravenously. The chest was opened by removing the 3rd and 4th ribs and sometimes in addition a sternotomy was performed. The pericardium was vertically incised and the heart was exposed. Then the electrodes were inserted and the heart was covered with a piece of gauze wetted with Ringer's solution.

2. Electrodes

Two types of electrodes were used: electrodes having multiple electrode terminals (multipolar electrode) and two electrode terminals (bipolar electrode). These electrodes were designed to meet the following requirements: they were to be non-polarizable, rigid, capable of being easily and accurately positioned and give a minimum amount of injury due to insertion.

The multipolar electrode (which was designed by Mizuno¹⁶⁾) was employed for the intramural recording from the interventricular septum and the ventricular free wall. The electrode consisted of 6 to 10 insulated copper wires of 70 microns in diameter, the end of the first wire being aligned a distance of 1 mm. from the end of a 120 microns diameter insulated copper wire shaft which provided support for these wires and the ends of the other wires being aligned a distance of 1 mm. from the first wire and from each other on the shaft, from the second through tenth wire respectively. These wires were fixed with Cashew lacquer as described above to the insulated copper wire shaft which was provided with an arrow-head (a piece of metal, 300 microns in diameter and 1.5 mm. in length) at its tip (Fig. 1). The entire electrode with

Fig. 1. This multipolar electrode consists of ten insulated copper wires (70 microns in diameter) aligned on a shaft of a 120 microns diameter insulated copper wire, which is provided with a hook at its tip to allow it to be supported on the bevel of the needle sheath (external diameter 1.0 mm.).

the exception of the arrow-head tip was protected within the sheath of an injection needle, 1 mm. external diameter and 50 mm. in length while being thrust through the ventricular free wall into the cardiac cavity. After the arrow-head had pierced the endocardial surface, the needle sheath then was withdrawn gently so as to leave the electrode terminals in direct contact with the myocardium, the arrow-head holding the tip of the shaft on the endocardial surface. In order to place the electrode in the interventricular septum, the needle sheath was thrust through the right ventricular free wall and further through the septum via the right ventricular cavity. Once the arrow-head had pierced the endocardial surface of the left ventricular cavity, the needle was withdrawn, the arrow-head holding the tip of the shaft on the left endocardial surface of the septum (Fig. 2).

Fig. 2. Upper: The insulated copper wires in place. The needle is thrust through the ventricular muscle into the cavity and then the injection needle is withdrawn so that each cut end of the insulated copper wires makes direct contact with the ventricular muscle at 1mm. intervals. The hook holds the tip of the electrode on the endocardial surface. Two electrodes are employed one for the ventricular free wall, and one for the interventricular septum. Lower: Contiguous bipolar and unipolar ECGs at the terminals of the electrode A.

N: Normal beat E: Extrasystole

The bipolar electrode consisted of two insulated copper wires of 100 microns in diameter which previously had been employed by Toyoshima and Mizuno¹⁴⁾, and Matsuoka¹⁷⁾ in their experiments. Both terminals of this electrode were fixed either at the endocardial or epicardial surface.

The resistance between two terminals of the bipolar electrode was approximately 30 to 40 kilohms and that of the multipolar electrode was about 80 to 120 kilohms. When a blood clot formed at a terminal, the resistance increased. To reduce the influence of the variability in the resistance the input impedance of the amplifier was enlarged. The resistance between the electrode terminals affects the low-frequency components to a large extent, but affects the high-frequency components to a lesser extent¹⁸⁾. It

was considered that this problem had only minor significance, however, in this series of experiments in which a contiguous bipolar lead ECG was used.

The electrode could be accurately positioned because of the arrow-head and was not likely to be bent since it was protected by the needle sheath; thus the operator was able to introduce the needle in the ventricular wall perpendicular to the epicardial surface rather easily. The local injury caused by the insertion of a needle with an external diameter of only 1 mm. was very slight causing an RS-T elevation which only lasted from 5 to 10 minutes.

To confirm that the position of the electrode did not alter during the experiment, the ECG pattern of each lead at the beginning of the experiment was compared with that at the end of experiment. The position of electrode was examined at an autopsy after the completion of each of the experiments.

3. Instruments and recording methods

The diagrammatic arrangement of the apparatus is shown in Fig. 3. The pre-amplifiers used are push-

vibrator. The recordings were made on photographic paper which was run at a speed of 20 to 30 cm. per second. For monitoring a four channel direct writing electrocardiograph was employed. The input impedance of pre-amplifiers was made high so as to minimize the influence of the variability in the resistance between the electrode terminals.

The free end of the insulated copper wires were terminated in a plunge box, which connects with the amplifier through a selector box thus allowing the operator to choose any combination of unipolar or bipolar leads within the multipolar electrode. Wilson's central terminal was used as indifferent electrode for unipolar leads.

Each of the insulated copper wires from the multipolar electrode was numbered in order from the tip to the base of the electrode, one through ten respectively. The polarity was connected in such a way that an upright deflection of a contiguous bipolar ECG would indicate that a lower numbered terminal was negative with respect to the one above it. Thus, an upright deflection would indicate that activation in the location of the lower numbered terminal occurred earlier than in the location of the higher numbered terminal (Fig. 2).

Lead II or a direct unipolar lead from the anterior wall of the right ventricle was used as the reference lead.

4. Stimulation

Electrical stimuli were employed exclusively to provoke ventricular extrasystoles. In the majority of the experiments, the stimuli were square waves which were initiated by a Nippon Kodon MSE-2 stimulator; in the minority, induction shocks produced by inductrium were used. The stimulus was a square wave, 2 milliseconds in duration, with the strength of 50 to 100 microamperes (approximately three times threshold).

Changes in excitability of the myocardium during one complete cardiac cycle affect the ventricular activation process¹⁹⁾. Thus, in order to study the activation process in extrasystole, it is necessary to give the stimulus at a certain interval during the cardiac cycle, and although it has been stated that induction shocks gave results qualitatively similar to those obtained using square wave pulses²⁰⁾, induction shocks are not suitable to place stimuli at a required interval during the cardiac cycle. The stimuli were induced by means of a specially designed synchronizer, which operated in such a way that the normal R wave coming

Fig. 3. Upper: Diagrammatic arrangement of the stimulating and recording apparatus employed in the experiments.
Lower: The circuit of the synchronizer.

pull with an input impedance of 2 megohms. This amplifier was used in conjunction with a Yokogawa three channel oscillograph mounted with an H-type

the moment after the knob-switch was pushed acted as triggering-signal to have the stimulator deliver a single square wave of any desired interval after the signal was produced (Fig. 3 Lower part). A contiguous bipolar lead was used for utilizing the R wave as the signal, because this lead renders a steep deflection and thus a well defined signal-point time. The stimuli were given at 200 to 300 milliseconds from the preceding normal R wave, for the supernormal phase is present during this period, when extrasystoles may be readily produced.

All the stimuli were discharged through contiguous bipolar electrodes. Reproducibility of the same ECG pattern from one stimulating focus was always checked to make sure of the constancy of the experimental milieu.

5. Determination of the arrival time of activation.

Lewis, in his studies on the process of ventricular activation, consistently used the intrinsic deflection of unipolar lead as the indicator of the arrival time of the activation wave⁴⁾. He took the top of the R wave as the time of excitation²¹⁾. Wilson and his associates, at first, abode by this principle²²⁾, but later took the nadir of S wave as the indicator instead²³⁾. Maekawa took the intersection of the intrinsic deflection with the isoelectric line as the point²⁴⁾, while Sodi-Pallares and his co-workers took the lower one third of the intrinsic deflection²⁵⁾.

Usually there is a significant difference in time between the summit of the R wave and the nadir of the S wave. Thus it is not unexpected for the different investigators to obtain varied results concerning the arrival time of activation. Durrer and his associates divided the intrinsic deflection into three components and considered the fast portion of the intrinsic deflection the time of excitation⁹⁾. In these experiments the presence of such portion also was observed; however, the intrinsic deflection of the unipolar lead did not manifest itself as a steep deflection, as reported by Eyster and Meek²⁶⁾, and Toyoshima and his associates²⁷⁾. Toyoshima and his associates demonstrated by experiments and mathematical analysis that the time of excitation lay somewhere within the intrinsic deflection, but its exact position was indeterminate. Sano and his co-workers²⁸⁾ recently have confirmed this fact by their experiments performed using the microelectrode technique. The downward deflection often is not steep, particularly in the case of the QS wave from the subendocardium or in the

case of extrasystolic deflection (Fig. 4).

Fig. 4. Left: Contiguous bipolar and unipolar lead ECGs of a normal beat recorded from the left endocardial surface of the interventricular septum. The curve of the bipolar lead has a sharp and narrow contour. Right: Contiguous bipolar and unipolar lead ECGs recorded from the epicardial surface of the ventricular free wall.
N: Normal beat
Es: Ventricular extrasystole

It is undoubtedly true that the unipolar lead ECG represents mainly the electric phenomenon occurring at the area adjacent to the electrode; Kisch²⁹⁾ held the view that the influence of extrinsic factors on the direct unipolar lead ECG negligible. The author does not agree with his premise, and it now has been well documented that the influence of the entire heart to this derivation is quite large. Since actually the unipolar lead ECG is greatly influenced by extrinsic factors, it is very difficult to define the exact position of the time of excitation from this type of lead. Scher and his associates³⁰⁾ stated that areas with similar wave shapes need not be simultaneously depolarized, since a continuous ring of myocardium in a homogeneous medium excited by a continually circulating activation wave at any velocity, would show the same potential shape at all points, and that time of local activity cannot be infallibly determined by measurements made on intramural records, particularly not by measurements on unipolar records which show both local and distant activity. Thus, in these experiments the unipolar lead was used merely adjunctively when needed, for by using this type lead it is very easy to obtain an overall picture of the activation process and to ascertain the position of the electrode point.

Harris³¹⁾ devised the contiguous bipolar lead and demonstrated that this derivation permits a much more accurate measurement of the time of excitation than the unipolar lead, because it is less influenced by distant areas. According to Itatsu's experiments and theoretical study³²⁾³³⁾, he took the summit of the main deflection of a contiguous bipolar lead as the indicator for the arrival time of activation. Durrer and his associates⁹⁾ also noted that the fast portion of the

intrinsic deflection of the unipolar lead corresponded to the vertex of the differential lead ECG. In view of the above considerations, the summit of main deflection on the contiguous bipolar lead as the indicator of the arrival time of activation was adopted in these experiments.

The contiguous bipolar lead permits the researcher to obtain the time relationship of the activation process rather easily, as this type lead is little affected by extrinsic factors and its main deflection remains unchanged, as long as there is no local injury. The ventricular activation process which is a three dimensional phenomenon is given two dimensional presentation by the contiguous bipolar lead; however, this type lead is still sufficient to enable one to infer the process of changing excitation within a restricted area.

In the recent investigations on the ventricular activations, this type of derivation has predominantly been employed.

Acceptance of the escaped current as the reference point of the measurement of the time of excitation was rejected, though it has been used in some previous investigations¹¹⁾. The latent time between the delivery of the stimulating impulse and beginning of the ventricular excitation varies during the cardiac cycle¹⁹⁾. To eliminate this variable, the onset of the reference lead ECG is preferred to the escaped current. The onset of the reference lead, however, is also imperfect in that it is subject to the problem of "ECG silence" and its configuration in extrasystole does not remain constant with different stimulating foci.

RESULTS

The multipolar electrode was inserted into either ventricular free wall (in the majority of the experiments, the left ventricular wall), and the interventricular septum.

Electrical stimuli were evoked either at the points adjacent to or distant from the electrode lead points where the activation waves due to the experimental extrasystoles were recorded with a contiguous bipolar ECG. The arrival times of the activation obtained thereof were used to analyse the process of ventricular activation.

1. THE VENTRICULAR FREE WALL

Similarly, as found in reports by other investigators, it was found that the activation wave spread from the apex to the base and from the endocardial to the epicardial side in normal beats.

With a multipolar electrode inserted in the mid portion of the left ventricular free wall, the arrival times of the activation at the electrode terminals were measured with relation to the activation waves either originating from the stimulation delivered at the various terminals on the electrode or at points adjacent to the electrode (Fig. 5).

When an activation wave due to an extrasystole originating in an area adjoining the recording electrode was received, the time required for the arrival of the activation wave was proportional to

Fig. 5. The arrival times of the activation in a normal beat and various extrasystoles at the individual terminals on the multipolar electrode A, inserted into a left ventricular free wall (the arrival times of the activation were measured from the ECG of contiguous bipolar leads).

- A: The polarity in the bipolar leads of an extrasystole from the stimulation A 1-2 is the same as the normal.
- B: The polarity in the bipolar leads of an extrasystole from the stimulation A 9-10 is reverse of normal.
- C: The polarity in the bipolar leads of an extrasystole from the stimulation B 2-3 is not definite.

N: Normal beat Es: Extrasystole

the distance between the ectopic focus and the receiving electrode. The extrasystolic activation wave propagated in all directions from the stimulating point. The activation wave originating from a sub-endocardial focus (A 1-2) traveled from the sub-endocardium toward the subepicardium, thus the polarity of each contiguous bipolar lead ECG was the

same as in the normal, whereas its form was not the same (Fig. 5-A). When the focus was located in the subepicardium (A 9-10), the polarity was the reverse of normal, indicating that the activation wave proceeded from the subepicardium to the subendocardium (Fig. 5-B). The conduction times between the neighbouring bipolar leads with subendocardial stimulation did not differ from those with the subepicardial stimulation. When a focus (B 2-3) in the subendocardium which was 8 mm. away from A 1-2 was provoked, the arrival times of the activation in the epicardial side were longer than those of the endocardial side, but the time lags between the neighbouring lead points were shorter than those in the case of stimulation A 1-2 and the polarity of each bipolar lead ECG was not well defined (Fig. 5C).

The conduction velocity was 30 to 50 cm. per second.

To observe these phenomena in three dimensions, three electrode needles were inserted in the ventricular free wall in such a way as to make an equilateral triangle and the stimuli were provoked from another electrode inserted in its center. The stimuli were evoked at both the subendocardial (O 1-2) and subepicardial (O 5-6) end terminals. The arrival times of activation due to each stimulus were proportional to the distance between the ectopic focus and the electrodes regardless of their locations (Fig. 6).

Fig. 6. The electrodes A, B and C inserted at the corners of an equilateral triangle. The electrode for stimulation (O 1-2: subendocardial stimulation, O 5-6: subepicardial stimulation) is inserted in its center. The excitation waves spread radially from the site of stimulation.

Next, the activation process in the left ventricular free wall was investigated with regard to the

excitation originating from distant foci, i. e., the right ventricular free wall or the interventricular septum.

When a focus in the subendocardium of the right ventricular wall was stimulated the bipolar ECGs, recorded at the electrode inserted in the left ventricular free wall, had the same pattern of polarity as the normal and all their arrival times were approximately 30 milliseconds longer respectively than those in the normal; however preserving the same interrelationship as in the normal

Fig. 7. Comparison of the arrival times of the activation in the left ventricular free wall in a normal beat with the times in an extrasystole originating from B in the subendocardium of the right ventricle. The differences between the arrival times at the neighbouring terminals in extrasystole are similar to those in normal indicating that the mode of spread remains unchanged.

(Fig. 7). When the subepicardial point corresponding to the above-mentioned subendocardial focus was stimulated, the results were almost identical.

By inserting two electrodes into the left ventricular wall, it was possible to examine the arrival times of activation at the corresponding electrode terminals on each electrode with respect to the extrasystole starting from the right ventricle. In many cases the time differences between the neighbouring electrode terminals were the same as in the normal (Fig. 8), but there were some cases showing

Fig. 8. Comparison of the activation processes along two electrodes (A and B) within the left ventricular free wall in a normal beat with the times in an extrasystole starting from the right ventricular free wall (C 1-2). The time relationship at the neighbouring terminals in extrasystole is similar to that in the normal.

Fig. 9. An experiment similar to that in Fig. 8. The differences between the times of excitation in extrasystole are similar to those in the normal along each electrode. The arrival times of activation at each corresponding terminal on A in extrasystole are 8 to 10 milliseconds longer than those on B, whereas no such a time lag is noted between A and B in the normal.

a different interrelationship (Fig. 9).

In a small number of cases, the arrival time in the epicardial side was not delayed as compared with the normal. Moreover, in some cases the polarity of the bipolar ECG A 5-6 was reversed (Fig. 10).

When the stimulating focus was in the inter-ventricular septum, the activation process in the left ventricular free wall was the same as in the case of right ventricular stimulation (Fig. 11). The

Fig. 10. An experiment similar to that in Fig. 7. The time relationship of the arrival times of activation at the electrode terminals in extrasystole is different from the normal. Notice that the polarity of the bipolar ECG of A 5-6 is reversed.

activation processes within the left ventricular free wall in the stimulations of the left (B 1-2) and right subendocardium (B 5-6) of the septum were compared. The activation wave formed by right subendocardial stimulation reached each terminal in the left ventricular free wall approximately 20 milliseconds later than the wave formed by left subendocardial stimulation. At the same time, the QRS duration of the reference ECG in right side stimulation was approximately 18 milliseconds longer than in left side stimulation.

The activation process of an extrasystole originating in the same ventricle was examined. Four electrodes A, B, C and D were inserted into the left ventricular free wall in that order from base to apex respectively. The activation processes at each electrode terminal in four different stimulations, A 1-2 (basal-subendocardial), D 1-2 (apical-subendocardial), A 5-6 (basal-subepicardial) and D 5-6 (apical-subepicardial) are shown diagrammatically in Fig. 12 in comparison with the normal beat. In the stimulation A 1-2, the excitation progressed from the endocardial to epicardial side in all four electrodes. In electrode B, which was located close to electrode A, the time relationship of the arrival time was entirely different from the normal beat, similar to those in Fig. 5, while the distant electrodes C and D showed the same time relationship

Fig. 11. Stimulation in the septum. The mode of conduction in this condition is similar to that in stimulation at the opposite free wall. The arrival times of the activation in a right subendocardial stimulation are 20 milliseconds longer at each terminal than those in a left subendocardial stimulation of the septum.

Fig. 12. Four electrodes A, B, C and D in the left ventricular free wall, as shown in the left upper diagram. The mode of conduction along each set of electrode terminals in four different stimulations, A 1-2, A 5-6, D 1-2 and D 5-6 are compared with that in the normal. Arrows show the direction of spread. Solid lines indicate that the mode of conduction was the same as the normal; broken lines indicate that it was different from the normal.

as the normal beat. In the stimulation A 5-6, the electrodes B and C showed that activation progressed from the epicardial to the endocardial side, the reverse of the normal beat. In electrode D the activation process proceeded from the endocardial to epicardial side having the same time relationship as in the normal. In stimulation D 5-6, electrode C, in the center, showed the activation wave made a double invasion from both the epi- and endocardial sides to the center.

2. THE INTERVENTRICULAR SEPTUM

The activation processes in the septum were studied with regard to two types of stimulation: stimulation within the septum and stimulation in the ventricular free wall.

As to the activation process in normal beats, the results were in fair agreement with the various investigations by Sodi-Pallares³⁴⁾ Burchell³⁵⁾ Scher¹³⁾ and their co-workers, Kimura³⁶⁾ and Toyoshima and Mizuno's¹⁴⁾ investigations. The normal activation wave in the septum proceeded from the left and right subendocardium interiorly toward the center and from the apex to the base. It required more than thirty milliseconds for the activation wave to reach the central upper part of the septum.

The activation wave due to stimulus in the subendocardium of the septum (A 6-7) spread toward the left unidirectionally, as polarity of the contiguous bipolar ECGs on the electrode needle A was negative throughout the whole thickness of the septal mass and the times of excitation were uniformly delayed toward the left (Fig. 13). That is, the bipolar ECGs recorded in the area where the normal activation proceeds from left-to-center showed a reverse polarity to the normal, while those recorded in the areas of right-to-center propagation remained the same as the normal in their polarity but differed in form.

Fig. 13. Spread in the septum of excitation due to stimulations at the right and left septal subendocardium and its comparison with the normal. Normal: Double invasion
Extrasystole: Unidirectional spread

The excitation due to stimulus originating in the left subendocardium of the septum proceeded unidirectionally from left to right.

The conduction velocity within the septum in the area close to the stimulating focus was 30 to 50 cm. per second.

The excitation originating in the left ventricular free wall spread from left to right unidirectionally within the septum (Fig. 14). At the electrode terminals 1 to 5 which were located in the area normally excited from left to right, the arrival times, polarity and form of bipolar ECGs were the same as in the normal, while at the 5-6 terminals which were normally controlled from the right side, the polarity became reversed and the arrival time as compared with the 4-5 terminals was considerably delayed. The excitation originating in the right ventricular free wall spread from right to left within the septum and had the negative polarity of all bipolar ECGs (Fig. 15). In the bipolar ECG between the lead points 3 and 4, where it is supposed the normal activation waves from the right and left endocardial surface in the septum encounter each other, the deflection is wide and diphasic, the vertex of this deflection coinciding with the main deflection of the 4-5 lead, the nadir of the deflection coinciding with the main deflection of the 2-3 lead, indicating that the time

Fig. 14. Spread within the septum of the excitation originating from the left ventricular free wall. The activation wave spreads from left to right, unidirectionally. The deflections of all the bipolar ECGs are upright.

Fig. 15. Spread of the excitation in the septum. Comparison of the spread within the septum of the excitation originating from the right ventricular free wall with the normal spread. The excitation spreads from right to left. Notice slower conduction of extrasystole at A 3-4.

required for conduction between the 4-5 lead and 2-3 lead was long; thus a considerable slowing of the conduction between the 3-4 lead is indicated.

In general, the intraseptal spread of the excitation originating in the ventricular free wall progresses unidirectionally from the side of stimulation to the opposite side and slowing of conduction in the area, where the activation waves from the right and left bundle branches normally encounter each other, was noted in many cases. In a small number of cases, however, the septum received a double invasion as in the case of free wall stimulation,

though this double invasion was not identical with the double invasion in normal beats (Fig. 16).

Fig. 16. An activation wave originating from the left ventricular free wall spreads from left to right; however, a double invasion occurs in the right side of the interventricular septum. Polarity and form of the bipolar lead ECG at A 5-6 remains the same as the normal and the activation wave reaches A 5-6 earlier than A 4-5.

DISCUSSION

Studies on experimental ventricular extrasystole were performed many years ago by Burden-Sanderson³⁷⁾ on the toad heart and by Kraus and Nicolai⁴⁾ on the canine heart. Both these investigators concluded that the activation wave due to ventricular extrasystole spread in all directions from the ectopic focus independently of the performed pathway. On the other hand, Lewis⁵⁾ stated that the activation wave of extrasystole similarly to the normal made fast endocardial conduction and thus must be conducted by a specialized conducting system. Scherf³⁸⁾ and many other investigators supported this view. These studies, however, were limited to recordings from the epicardial surface and did not permit detailed analysis.

Recently, Durrer⁹⁾⁻¹¹⁾ and Scher¹²⁾¹³⁾ and their co-workers studied the process in the mammalian heart using an intramural electrode technique. In their experiments, the study was limited to the focus-sided free wall and the interventricular septum and did not cover the whole picture of excitation throughout the entire heart. In the analysis of this data, emphasis is placed on this point.

The arrival time of activation of extrasystole in the area adjoining the ectopic focus is delayed in proportion to the distance between the electrode and focus. The form and polarity, of the conti-

guous bipolar ECG at each pair of lead points, are not the same as the normal beat.

In the case of subendocardial stimulation (Fig. 5-A) the deflection recorded at A 3-4 for the stimulation at A 1-2 was wider and its potential was higher than a normal beat received at the same bipolar lead. The polarity was the same as normal. This finding suggests that the excitation due to extrasystole at this site A 3-4 was conducted by the proper cardiac muscle, whereas the normal excitation was predominantly conducted by Purkinje fibers. In contrast, in the A 5-6 and A 7-8 located in the subepicardium, the configuration and duration of the deflection remained unchanged in extrasystole. The difference between the arrival times of A 5-6 and A 7-8 also remained the same. Thus, in this area, the excitation wave is transmitted by the proper muscle both in normal systole and extrasystole.

When the stimulus is delivered at the subendocardial terminal, the velocity from endocardium to epicardium along a electrode is approximately equal to the reverse direction when the subepicardial terminal is stimulated. This result agrees with Scher's report¹²⁾, but disagrees with Yamada's experiments³⁹⁾ that were performed with the toad heart. This discrepancy was thought to be attributable to the difference in the method and animals used.

The activation wave due to extrasystole, in a small area adjacent to the focus, wherever the focus may be located, spreads radially indifferent to the Purkinje fibers, i. e., by muscle conduction. Durrer's observation¹⁰⁾ that the reversal phenomenon which is present in the normal beat disappears in ventricular extrasystole is assumed to be due to this same mechanism.

The velocity of the transmural conduction in extrasystole was 30 to 50 cm. per second the same as the velocity of normal systole. This value agrees well with Durrer's¹¹⁾ and Scher's¹²⁾ results which were obtained from intramural ECG. No local difference in the velocity was found.

The reason that Purkinje fibers are indifferent to the conduction in a small area adjacent to the focus may be explained on the basis of the fact that the refractory period of the specialized conducting system is longer than the proper cardiac muscle, rather than on the basis of the impossibility of retrograde conduction from the ordinary cardiac

muscle to the Purkinje fibers⁴⁰).

A considerable delay of conduction was noted at the area adjacent to the stimulating focus similarly to Scher's observation¹²). There are two possible explanations for this phenomenon, i. e., slow conduction because of the presence of the partial refractoriness in the adjacent area or because of the presence of latency. The results of these experiments did not permit a decision as to which of these two was the true mechanism.

The ventricular activation process of an area distant from the extrasystolic focus is different from that in the area adjacent to the focus. Even in the case of subepicardial stimulation, the activation wave proceeded from endocardium to epicardium as in the normal excitation. This evidence clearly indicates that a specialized conducting system is responsible for the conduction. This mechanism has been postulated by Lewis⁵) and supported by Scher's experiments¹²). An attempt was made to examine this point in greater detail, the results being shown diagrammatically in Fig. 12. In the case of subendocardial stimulation A 1-2, the time relationship of the arrival times at each terminal on the distal electrodes C and D were the same as the normal, indicating that the activation process along these two electrodes occurred with the same mode as in normal systole and the Purkinje fibers were being involved. In the case of subepicardial stimulation A 5-6, while the activation process along the electrodes B and C progressed from epicardium to endocardium in reverse to the normal, the activation process along the far-distal electrode D was the same as the normal indicating that the activation proceeded in the endo-epicardial direction via the Purkinje fibers. On the other hand, in the case of stimulation D 5-6, the activation showed a double invasion along electrode B.

Thus, it was concluded that the activation wave due to extrasystole was transmitted partly by muscle conduction and partly by the Purkinje fibers: the former playing the major rôle in the area adjacent to the ectopic focus (circular area 1 to 1.5 cm. from the focus) and the latter in the more distant areas.

The mode of activation process as whole (not limited to the area along one particular electrode) in extrasystole originating in the opposite ventricular free wall was similar to that of the normal in most of the cases (Fig. 7 and 8): however, in

some case as seen in Fig. 9, the mode of activation on one electrode was similar, whereas the time relationship, between the arrival times of the corresponding electrode terminals on two different electrodes, was different from the normal. Also in a small number of cases, as seen in Fig. 10, the excitation proceeded in reverse to the normal at A 5-6 located in the area near the subepicardium. This phenomenon was interpreted as follows: even though the activation along each electrode is identical with the normal, each set of Purkinje fibers controlling the area of each electrode is activated in a different order from the normal, and also in the subepicardium where the distribution of Purkinje fibers is not denser, it is possible to conceive that some small area can be controlled by a different set of Purkinje fibers than in the normal. This explanation is somewhat similar to those offered by Drury and Mackenzie⁴¹), but different from the view that the activation process which started in the opposite ventricular free wall is entirely identical with that of normal systole, which has been supported by Lewis⁵), Sodi-Pallares⁴²) and other investigators.

Very little research has been done on the activation process of ventricular extrasystole within the septum, because of its anatomical position which makes study difficult. Toyoshima and Mizuno¹⁴), and Scher and his co-workers¹³) studied this only with regard to extrasystole started from the intra-septal foci. Because of the peculiarity in the distribution of the Purkinje fibers in the interventricular septum, the activation in extrasystole is also complicated in the septum in contrast to that in the ventricular free wall.

The activation wave originating from an intra-septal focus is conducted in the area adjacent to the focus in a way similar to conduction in the ventricular free wall, i. e., from the focus in all directions with a velocity of from 30 to 50 cm. per seconds independent of the Purkinje fibers.

The excitation originating from the ventricular free wall reaches the septum through the specialized conducting system, then the region which is controlled by ipsilateral bundle branch is activated in the same mode as in normal systole and the region which is controlled by the contralateral bundle branch is activated in a reverse direction from the normal systole, that is, the activation wave progresses unidirectionally from the focus side to the

opposite side in most cases.

As shown in Figs. 14 and 15, in the region where it is supposed that the normal activation waves from the right and left bundle branch encounter each other, a considerable slowing of the conduction was often noted. The cause of this delay is thought to be due to the fact that the rapid conduction through the Purkinje fibers is replaced by the slow conduction of the muscle. It is also possible to explain this delay by the slow conduction at the "muscular boundary to conduction" which is present between the right and left septal masses. Sodi-Pallares⁴²⁾ held the view that such delay occurred at a small restricted area in the septum, as in the case of bundle branch blocks⁴³⁾. There were no results to support this view in these experiments.

Previously it was believed that the activation wave which arrived at the septum through the Purkinje fibers proceeded retrograde the ipsilateral bundle branch up to the His' bundle, then spread to the opposite free wall through the contralateral bundle branch. Scherf⁴⁴⁾ observed that the experimental bundle branch block produced on the side of extrasystole did not modify the pattern of unipolar ECG. In these experiments it also was noted that the activation process in extrasystole originating below the side of block was not modified by the presence of a bundle branch block⁴⁵⁾.

The fact that the activation process in extrasystole from the opposite-side free wall had a different mode from the normal in spite of being conducted via Purkinje fibers may be largely attributed to the spread in the septum. That is, the intervention of muscle conduction in transmitting the activation for one bundle branch to another occurs at all levels of the septum and makes the order of activation of the opposite Purkinje fibers different from the order in the normal activation. Although there are no definite data to deny that the activation wave of extrasystole should reach the main bundle, it is concluded from the above stated results, that the main pathway of the intraseptal spread is a combination of muscle conduction and the conduction through Purkinje fibers, and not by the main bundle alone, though such a conduction may occur.

In 1928 Wahlin⁴⁶⁾ reported that in the bovine heart there is a septal connection between the bilateral Purkinje fibers. Alfredson and Skyes⁴⁷⁾ sup-

ported this observation on the basis of an experiment in which the cutting of one bundle branch produced prolongation of the QRS complex by only 0.01 second. Although this connection, of course, is not found in a dog or human heart, in which even the specialized conducting system is not recognized anatomically⁴⁸⁾. Rothberger⁴⁹⁾ stated that such a connection plays an important rôle in the activation process in a bundle branch block and in extrasystole. The hypothesis is quite convenient for the analysis of ventricular excitation in extrasystole; however, as far as these results are concerned, this hypothesis was not supported. If there is a site where the Purkinje fibers from both the bundle branches encounter each other in close proximity, conduction from the focus side to the opposite side should require relatively little time. This situation may be considered "functional transseptal connection".

Pruitt and co-workers⁵⁰⁾ supported Glomset's anatomical research⁴⁸⁾, which stated that there is no specialized conducting system in the human or canine heart, on the basis of their observation that the conduction velocity is related to the direction of muscle fibers and the subendocardial fast conduction is not by the specialized conducting system but by the direction of muscle fibers. Robb and Robb⁵¹⁾⁵²⁾ also stated that the activation process is dependent on the direction of the muscular bundle. From these experimental results, it was concluded that the ventricular activation process is not dependent on the course of muscle fibers. This conclusion agrees with Scher's⁵³⁾ and Sodi-Pallares'⁴²⁾ reports.

Although the presence of "the specialized conducting system" is now not established anatomically, from these results its presence should not be denied electrophysiologically.

From the experiments performed using intracellular microelectrodes the difference of proper cardiac muscle and specialized conducting tissue is recognized⁵⁴⁾.

Clinically the QRS complex in ventricular extrasystole manifests itself widely and in a bizarre way. This peculiar configuration may be explained with regard to the activation process in extrasystole. According to Schaefer⁵⁵⁾, the reversal of the direction of spread by only as much as 5 per cent of the entire muscle mass produces an 100 per cent change in the QRS complex in its time-potential

(QRS Fläche). It was concluded that the abnormal depolarization is a combined product of the slow conduction near the ectopic focus, followed by the difference in the order of the activation of the Purkinje fibers.

The unipolar ECG of ventricular extrasystole is manifested as the QS wave in the area adjacent to the ectopic focus, and the height of the R wave increases with an increase of the distance from the focus (Fig. 17). This agrees with the reports by other investigators¹⁵⁾. The detailed analysis of this derivation will be presented in another report.

Fig. 17. The schematic patterns of unipolar ECGs in the normal (left) and extrasystole (right). St.: Stimulating focus

SUMMARY AND CONCLUSIONS

1. The activation processes in experimentally produced ventricular extrasystoles in the canine heart were investigated using a multipolar electrode with regard to the ventricular free wall and the interventricular septum. A stimulator was used in conjunction with a synchronizer, which permitted the stimulus to be delivered at a constant interval during the cardiac cycle, thus eliminating the influence of change in the excitability of the myocardium during one cardiac cycle.

2. The summit of the main deflection of the contiguous bipolar lead was adopted as an indicator of the arrival time of activation, since it is little affected by extrinsic factors.

3. The excitation evoked in the ventricular free wall or the interventricular septum, is conducted only by the proper muscle in the area adjacent to the focus, and then is conducted by some specialized conducting system to the distant areas. The velocity of the muscle conduction was from 30 to 50 cm. per second. No local variability was found in the velocity.

4. The activation wave originating from the ventricular free wall, after arriving at the septum, is relayed by means of muscle conduction from the "focus-side" Purkinje fibers to the adjacent "op-

posite-side" Purkinje fibers, and then spreads to the opposite ventricular free wall by means of these fibers. It was inferred that in this last phase of conduction, the order of activation of the Purkinje fibers differed from the order in normal activation.

5. In the interventricular septum, a considerable slowing of the conduction was often noted in the region where it is assumed that the normal activation waves from the right and left bundle branches encounter each other; however, this region was not limited to a small area.

6. The direction of the muscle fibers is not related to the conduction velocity and does not affect the ventricular activation process.

7. The wide and bizarre QRS complex in ventricular extrasystole may be explained by the following two main factors: 1. slow conduction in the area adjacent to the focus and 2. different order of activation of the Purkinje fibers.

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