

Total Excitation of the Isolated Human Heart

By DIRK DURRER, M.D., R. TH. VAN DAM, M.D., G. E. FREUD, M.D.,
M. J. JANSE, M.D., F. L. MEIJLER, M.D., AND R. C. ARZBAECHER, PH.D.

SUMMARY

To obtain information concerning the time course and instantaneous distribution of the excitatory process of the normal human heart, studies were made on isolated human hearts from seven individuals who died from various cerebral conditions, but who had no history of cardiac disease. Measurements were made from as many as 870 intramural terminals.

In the isolated human hearts three endocardial areas were synchronously excited 0 to 5 msec after the start of the left ventricular activity potential. These areas increased rapidly in size during the next 5 to 10 msec and became confluent in 15 to 20 msec. The left ventricular areas first excited were (1) high on the anterior paraseptal wall just below the attachment of the mitral valve; (2) central on the left surface of the interventricular septum and (3) posterior paraseptal about one third of the distance from apex to base. The last part of the left ventricle to be activated usually was the posterobasal area. Endocardial activation of the right ventricle was found to start near the insertion of the anterior papillary muscle 5 to 10 msec after onset of the left ventricular cavity potential. Septal activation started in the middle third of the left side of the interventricular septum, somewhat anteriorly, and at the lower third at the junction of the septum and posterior wall. The epicardial excitation pattern reflected the movements of the intramural excitation wave. Conduction velocity was determined in one heart by an appropriate stimulation technic. Atrial excitation, explored in two hearts, spread more or less according to concentric isochronic lines.

Control studies, carried out on five canine hearts, disclosed that the pattern of ventricular excitation did not change after isolation and perfusion. However, total excitation was completed earlier in the isolated heart, and conduction velocity increased.

Careful mapping illustrations are presented.

Additional Indexing Words:

Ventricular excitation Intramural conduction velocity Epicardial excitation
Atrial excitation

KNOWLEDGE of the time course and instantaneous distribution of the excitatory process of the normal human heart would be of value for an understanding of the QRS complex.

Studies of this process during surgical intervention for heart disease or pulmonary

disease were restricted to the epicardial surface and mostly only to those parts which were easily accessible.

Some insight could be obtained about intramural excitation by the introduction of one or two intramural electrodes during surgical intervention. The data obtained in this way were of course very limited. It was evident from the beginning that in order to obtain data about all parts of the heart, we had to study the isolated heart, a method

From the University Department of Cardiology and Clinical Physiology, Wilhelmina-Gasthuis, Amsterdam, The Netherlands.

Investigation was supported by grants of the Netherlands Organization for the Advancement of Pure Research (Z.W.O.), The Hague, The Netherlands.

Presented in part by D. D. at the George E. Fahr Memorial Lecture, University of Minnesota, Minneapolis, Minnesota, February 1970.

Address for reprints: Dr. D. Durrer, Dept. of Cardiology and Clinical Physiology, Wilhelmina-Gasthuis, 1^e Melmerstraat 104, Amsterdam, The Netherlands.

Received October 14, 1969; accepted for publication December 1, 1969.

indicated in 1918 by Boden and Neukirch¹ and used incidentally in intervening years.^{2, 3}

Methods

Hearts were obtained from seven individuals who had died from various cerebral conditions and had no previous history of heart disease. Electrocardiograms taken several hours before death showed no evidence of cardiac disease. The hearts were removed within half an hour after death, the criterion for which was cessation of cardiac activity. Shortly before removal of the heart 10 mg of heparin was injected into the caval veins and massaged into the heart. The hearts were transported while immersed in an oxygenated modified Tyrode solution at 37 C. The aorta was cannulated and attached to a Langendorff perfusion apparatus. During the first 10 minutes the heart was perfused with oxygenated, heparinized, modified Tyrode solution in order to rinse out all remaining blood constituents; thereafter, for the entire duration of the experiment, the same perfusion fluid was used, to which a suspension of washed bovine erythrocytes had been added. The composition of this fluid was: Na, 149.1; K, 4.7; Ca, 2.6; Mg, 2.1; Cl, 137.6; HCO₃, 20.2; H₂PO₄, 0.7 mEq/L; hemoglobin, 3 g%; and glucose, 2 g/L. In the last two experiments also a 3% electrolyte-free Haemaccel R (Hoechst) solution and 20 γ /L of epinephrine were added. The solution was aerated by a mixture of O₂ and CO₂. PH was frequently checked and maintained at 7.35 ± 0.05 . Temperature was kept at 37 ± 0.5 C. Most hearts resumed beating spontaneously within the first 5 minutes of perfusion; in three cases electrical defibrillation was employed because of ventricular fibrillation. The hearts continued beating in a spontaneous sinus rhythm for a period ranging from 4 to 6½ hours.

Recording

The electrical activity of the heart was recorded from epicardial and intramural electrodes that were connected via a connector assembly unit to a Master selector switch board developed by the Laboratory of Medical Physics of the University of Amsterdam. This selector switch enabled us to connect any of 660 electrode terminals to the input stages of the recording units or to the output of a stimulator. Via a low capacitance cable the selector switch was connected to a pre-amplifier system, consisting of a modified DAS 100 system. Unipolar and bipolar leads were tape recorded on a 14-channel Ampex FR 1300 physiologic tape recorder at a tape speed of 15 inches/sec, monitored on an additional 8-channel Knott oscilloscope (type SGM 43) and printed on-line on a 14-channel

Elema inkwriter (type EMT 160).

In unipolar recordings, the indifferent electrode was placed on the root of the aorta. Perfusion apparatus, fluid bath, and recording and stimulating instruments were properly grounded at a common terminal. All complexes were recorded together with two fixed reference leads; one consisted of a unipolar lead from a special electrode introduced into the left ventricular cavity, the other was a selected unipolar intramural complex. As a rule all epicardial recordings were done with the apex of the heart immersed in a surrounding bath filled with perfusion fluid. For intramural recordings the heart was usually totally immersed in this bath.

Analysis

For the analysis the tapes were played back at a speed of 1½ inches/sec and the complexes were printed out on the Elema writer running at maximal speed. This resulted in an effective writing speed of 960 mm/sec, giving a time resolution of better than 1 msec. The fast part of the intrinsic deflection in the unipolar complexes was taken as the moment of activation at a given terminal. All activation times were expressed in milliseconds following the onset of left ventricular depolarization, as witnessed by the departure of the unipolar left ventricular cavity potential from the base line. In every record the zero time was checked with the intramural reference complex; their time relation varied not more than 3 msec in all data to be presented here. For every terminal at least 10 consecutive identical complexes were recorded; time measurements were carried out in duplicate or triplicate. Control records of one multi-electrode needle were carried out at intervals of approximately 1 hour throughout every experiment; only data obtained with unchanged control records were taken into consideration.

Epicardial Exploration

Unipolar and bipolar epicardial complexes were recorded from the ventricular surface by means of a hand-held electrode containing two silver terminals of 0.5-mm diameter, mounted 2-mm apart on a flat surface. This electrode was applied at numerous sites of the epicardial surface that were carefully noted on a map drawn during the experiments on which anatomic landmarks, such as coronary blood vessels, were entered. These maps were later compared with colored photographs of the heart taken at various angles. The final illustrations were drawn from these photographs.

For the exploration of the atrial surface a small electrode containing five terminals in a straight line was used, each terminal having a diameter of 0.1 mm, and the interterminal distance being 1

mm. As a time reference a bipolar complex from an electrode-pair sutured to the base of the right atrial appendage was included in every record from the atrial surface. Great care was taken to exert minimal pressure, since excessive pressure immediately would result in injury effects, which might influence the course of activation.

Intramural Exploration

Multi-electrode needles, carrying 10 or 20 platinum terminals, of 0.1 mm diameter each,⁴ interterminal distance being 2 mm, were introduced into the wall of both ventricles. In the first heart the multi-electrodes were inserted without any prearranged pattern. This presented considerable difficulties in the spatial analysis of electrode positions; even after resorting to stereographic x-ray tomography we were unable to locate some of the multi-electrode needles. Therefore, the following procedure was developed. The heart was positioned in such a way that a virtual axis connecting the middle of the mitral orifice and the apex of the left ventricle ran vertically. This was accomplished by fixing the apex to a suction cup, 1.5 cm in diameter, which could be positioned at will and could move freely in the vertical direction, allowing systolic displacement of the apex. Around the heart, a horizontal Plexiglas disc was mounted, which could be moved along a vertical scale. This disc carried a 360° scale, and its center was brought to coincide with the vertical axis of the left ventricle. With the aid of this disc intramural electrodes were inserted in horizontal planes at intervals of 45°. Slight variations were sometimes necessary to avoid puncturing coronary vessels. The disc was moved vertically along the heart at 1-cm intervals; thus, eight or nine horizontal planes were constructed. The equiangular placement of the needles in horizontal planes automatically provided alignment in vertical planes. In each heart up to 72 intramural multi-electrode needles were inserted in this way.

To avoid anatomic distortion due to contracture and shrinkage of muscle fibers, the heart, at the end of the experiment, was fixed in a diastolic shape by the following method. The heart was depolarized by adding KCl to the perfusion fluid. The cavities were drained by suction, and filled with molten beeswax. The heart with the needle electrodes in position was immediately transferred to a cold room (−4 C). The following day the heart was photographed from all sides, and the electrodes were replaced by stainless steel marker pins which were inserted with little or no difficulty into the same puncture canals. The heart was then deep frozen and later cut into slices along the original horizontal planes. The

sections were photographed and the puncture canals identified. From these photographs scale drawings were made in which eventually the activation time of each terminal was noted. Comparison of the anatomic position and electrical activity of those terminals situated just inside the ventricular cavity yielded a marked consistency.

Control Experiments

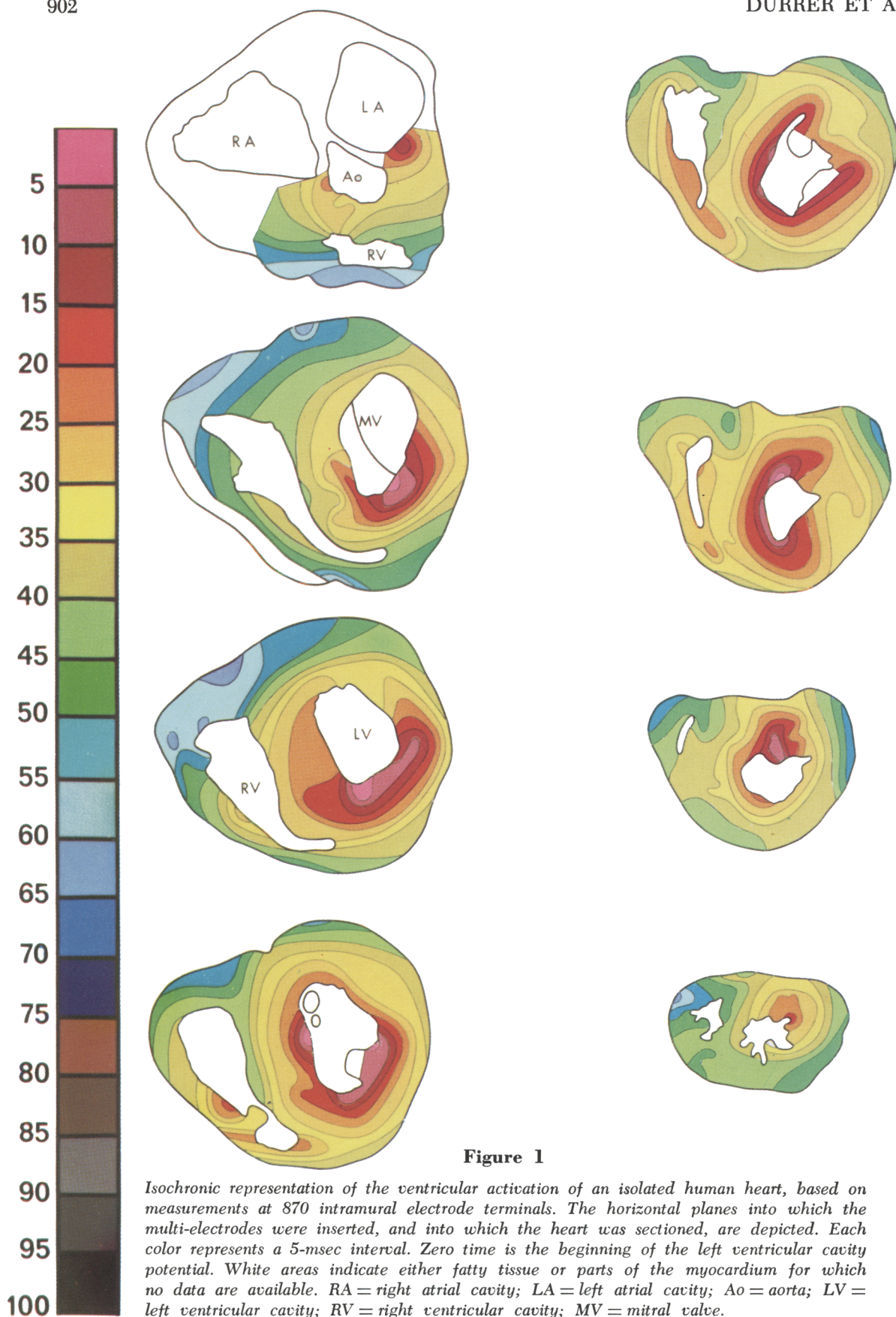
Control experiments in canine hearts were carried out to determine whether isolation and perfusion of the heart influenced the excitation of the ventricle. Five mongrel dogs, weighing 18 to 24 kg, were anesthetized with Na-pentobarbital (30 mg/kg). A midsternal thoracotomy was performed, and the heart was exposed. Multi-electrode needles were inserted into the ventricular wall, in one or more planes running parallel to the atrioventricular sulcus. Unipolar leads from and bipolar leads between consecutive intramural electrode terminals were recorded during normal sinus rhythm. When the recordings were completed, 1 ml of heparin was injected intravenously, and the heart was isolated and attached to the perfusion apparatus. The perfusion fluid was the same as that used for the perfusion of the human hearts. The multi-electrodes remained in their position, and half an hour after the beginning of perfusion the same recordings were made. In three dogs, slight suprathreshold stimuli were applied sequentially to the subepicardial terminal of each multi-electrode both prior to and after isolation of the heart. The stimuli were given 300 msec after a normal beat, and therefore, fell well outside the relative refractory period. The component of conduction velocity along the needle was measured in the following way: From bipolar leads between consecutive terminals of the stimulating needle electrode, the moments of activation of each terminal were measured; this resulted in a large number of values indicating the time needed for the activation front to pass from one terminal to another, located 2 mm further. The values for the *in situ* heart and for the isolated heart were compared, and the differences were statistically analyzed.

Results

Overall Pattern of Ventricular Excitation

Left Ventricle

The data obtained from four hearts demonstrate consistently that three endocardial areas were synchronously excited 0 to 5 msec after the start of the left ventricular cavity potential: (1) an area high on the anterior paraseptal wall just below the attachment of the mitral valve, extending at least 2 cm



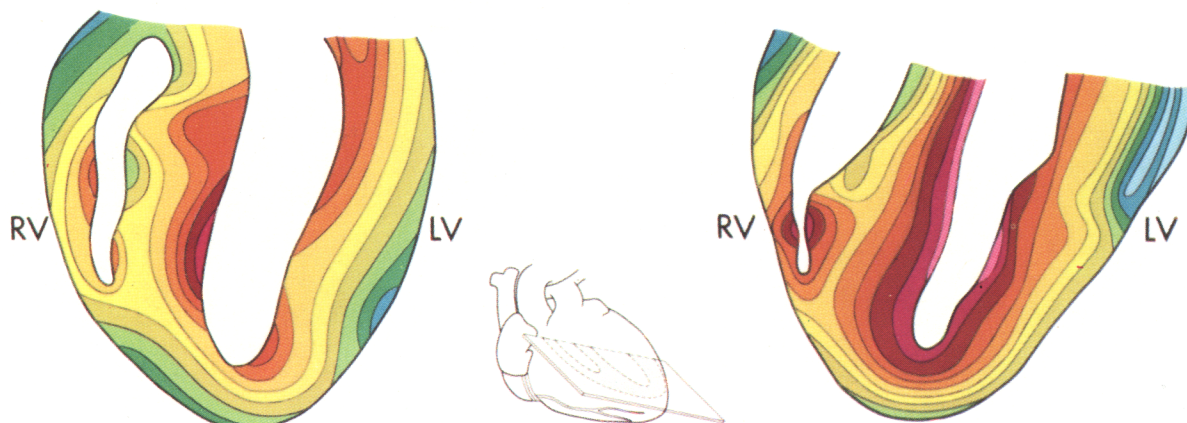


Figure 2

Nearly identical sections of two different human hearts. Inset shows how the sections were made. The color scheme of the isochronic areas is the same as in figure 1. RV = right ventricle; LV = left ventricle.

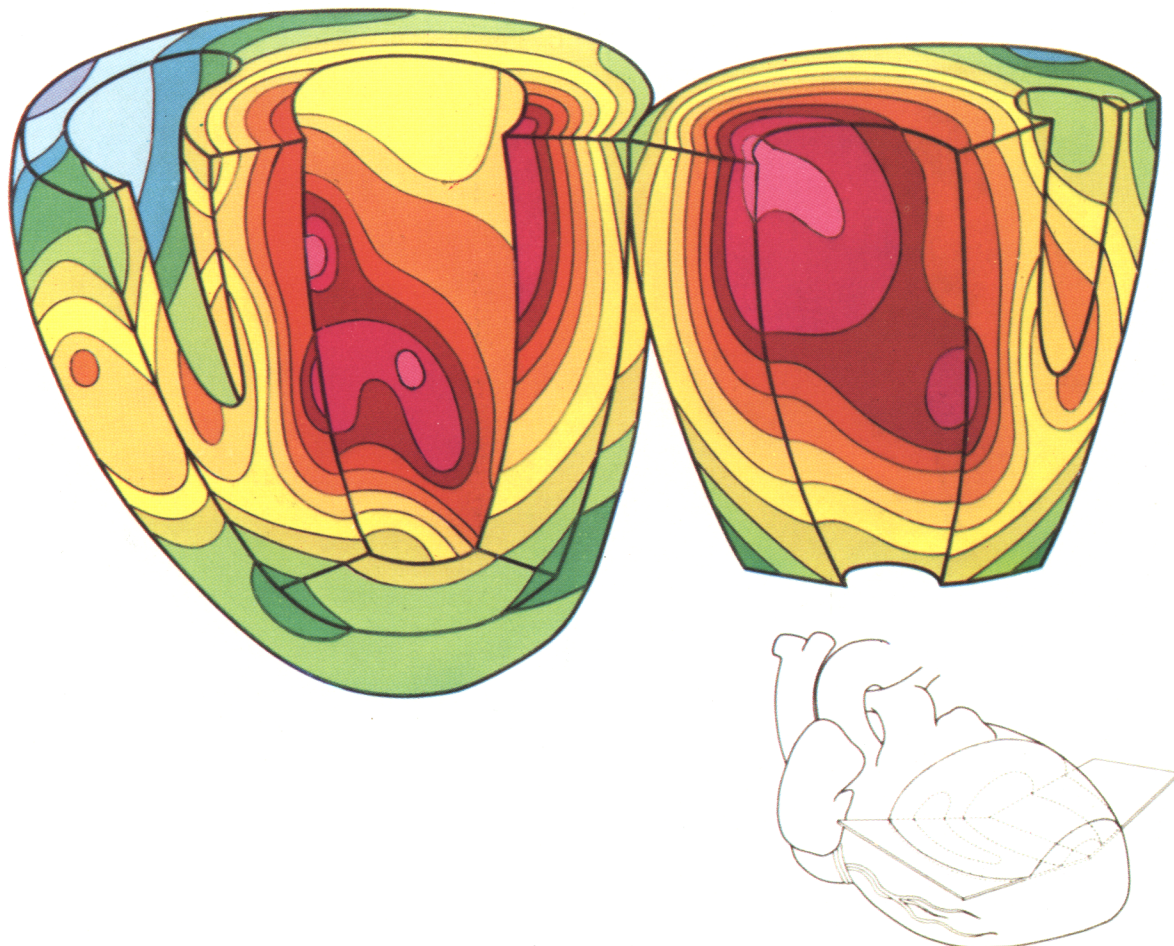
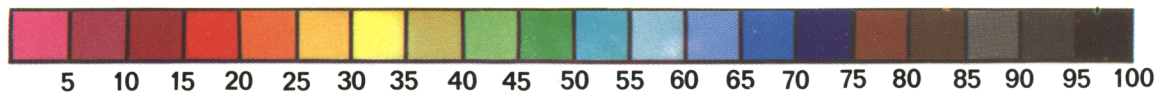
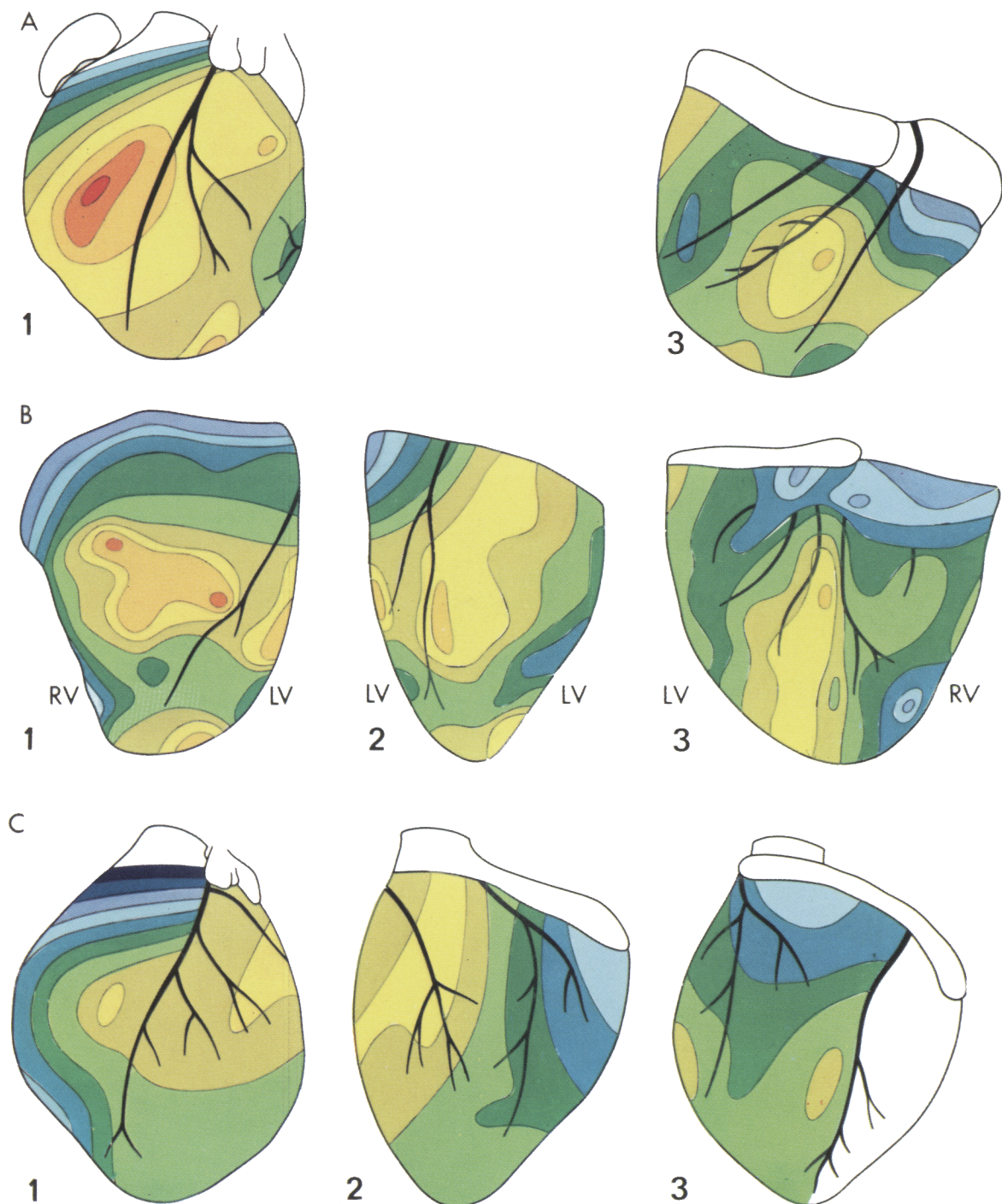


Figure 3

Three-dimensional isochronic representation of the activation of the same heart as in figure 1. Inset shows section levels. Color scheme identical to the one in figure 1.





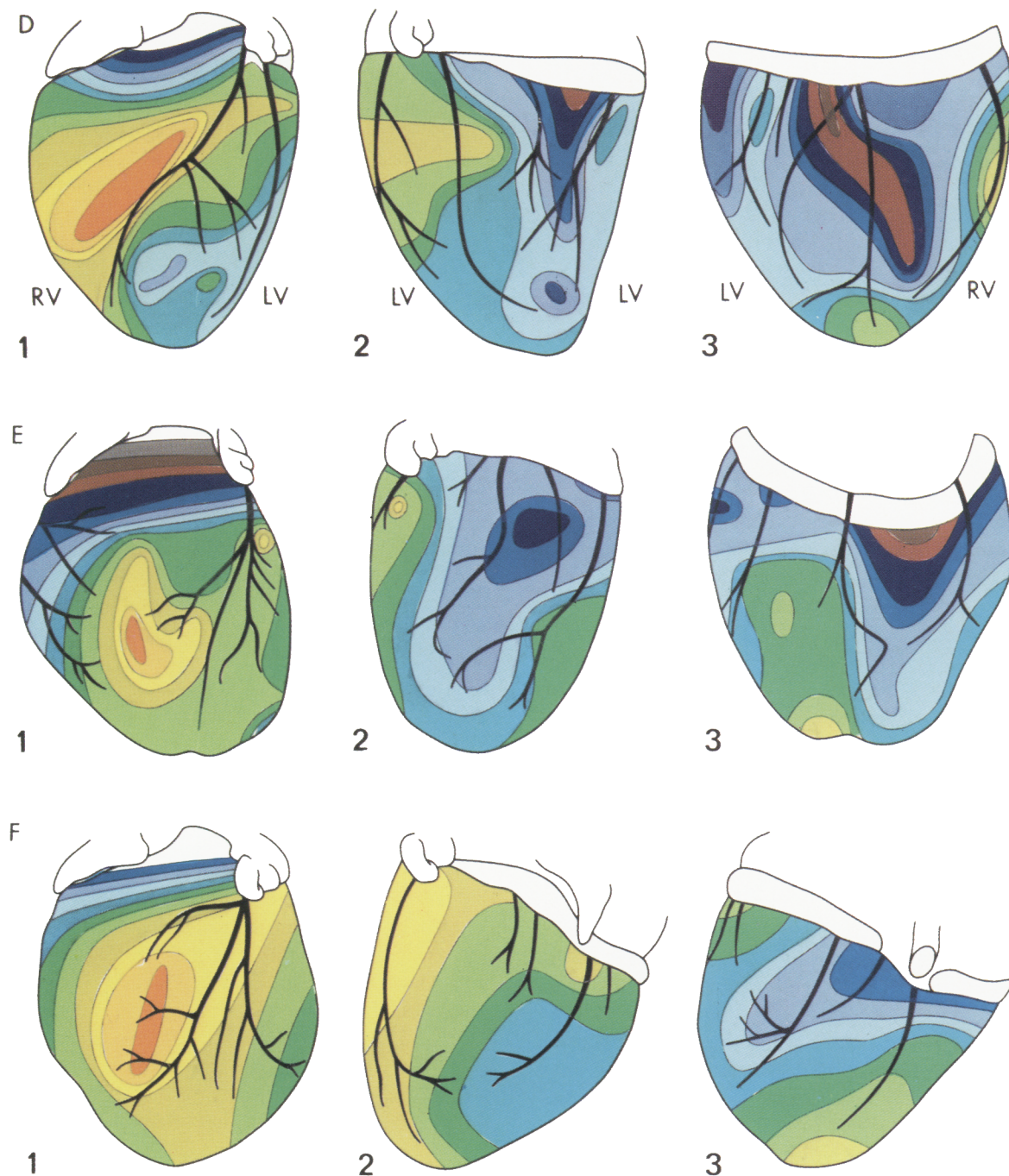
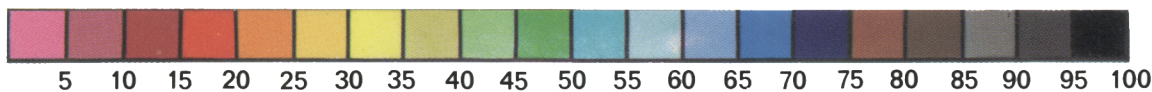


Figure 4

Epicardial excitation pattern of six different human hearts (A to F). In A only an anterior (1) and a posterior view (3) are shown; all other hearts are presented in an anterior view (1), a left lateral view (2), and a posterior view (3); some degree of overlapping occurs between the different views. RV = right ventricle; LV = left ventricle. The color scheme is the same as in figure 1.



toward the apex into the region of the anterior papillary muscle; (2) a central area on the left surface of the interventricular septum; (3) the posterior paraseptal area at about one third of the distance from apex to base.

These activated areas increase rapidly in size during the next 5 to 10 msec, becoming confluent at 15 to 20 msec after the onset of excitation. At this time the activation front envelops a great part of the ventricular cavity except for a posterobasal area, a middle lateral area and an apical anterior area. This movement around the cavity is much more rapid than the spread toward the epicardium. As activation continues individual variation from a general pattern increases. A nearly completely closed front is present after 30 msec, except at the posterobasal area. At this time, excitation has already reached the epicardial surface of those sites overlying the areas of earliest endocardial excitation. Activation continues to move to the epicardial surface in the other areas according to more or less concentric isochronic lines. The latest part to be activated is the posterobasal area; in some hearts it is the posterolateral area.

Right Ventricle

Endocardial activation starts near the insertion of the anterior papillary muscle about 5 to 10 msec after the onset of the left ventricular cavity potential, or slightly later. Then rapid invasion of the septum and the adjoining free right ventricular wall occurs and results in epicardial breakthrough in the area pretrabecularis after about 20 msec. The isochrones are not concentric, but rather, activation proceeds in a regular, more or less tangential way, reaching ultimately the pulmonary conus (at 60 to 70 msec) and the posterobasal area (at 60 to 70 msec).

The Interventricular Septum

Activation starts on the left septal surface in the middle third part, somewhat anteriorly, and at the lower third part at the junction of septum and posterior wall. In general, activation proceeds from left to right, and in an apical-basal direction. A right-to-left contribution is present in a varying degree, in the

anterior half of the middle third part, activity on the right septal surface always being later than earliest activity on the left septal surface. The crista supraventricularis is activated late; in the two hearts on which detailed information about the septal half of the crista supraventricularis can be given, excitation proceeded from the left side to the right, merging after about 45 msec with a front reaching the crista through the free wall of the right ventricle.

Figure 1 illustrates the overall pattern of ventricular excitation, as it was determined in one heart, based on measurements at 870 intramural terminals. The figure shows the horizontal electrode planes into which the heart had been sectioned. This is an isochronic representation in which each color corresponds to a unique 5-msec interval. In figure 2 nearly identical vertical sections of two different hearts are shown. Noteworthy features of this figure are the different contribution of right to left septal activation in the two hearts, the tangential spread of activity in the wall of the right ventricle, and the activation of the crista supraventricularis. In figure 3 an attempt has been made to visualize the pattern of activation in a three-dimensional presentation of the same heart as in figure 1.

Epicardial Excitation

The epicardial excitation pattern reflects the movements of the intramural excitation wave. The pattern of epicardial excitation of the hearts of six individuals of 19, 20, 29, 40, 40, and 53 years of age is depicted in figure 4. Early epicardial breakthrough occurred in the area pretrabecularis of the right ventricle in the 20 to 25-msec interval. From that area a more or less radial spread toward apex and base occurred, with latest excitation of the A-V sulcus region and pulmonary conus. The latest part to be activated was the posterobasal area of the right ventricle. Larger variations were visible in the epicardial excitation pattern of the left ventricle. Three early points of epicardial breakthrough were found: (1) a small area on the anterior surface paraseptally close to the A-V sulcus; (2) an anterior paraseptal area located halfway between apex and base, and

(3) a posterior paraseptal area, about halfway between the apex and base. In some hearts a small area of early breakthrough was found near the posterior apex. The location of the latest activated areas differed. Generally, the posterobasal left paraseptal region was the last activated part; in some hearts, however, a more lateral location was found.

Intramural Conduction Velocity

In one heart, conduction velocity was determined by driving the heart by a short train of stimuli delivered first at the subepicardial and then at the subendocardial terminal of a total of 22 multi-electrode needles. The stimuli were slightly suprathreshold; the frequency of the stimuli was slightly above the rate of the spontaneous sinus rhythm. In the case of intraseptal needles, the stimulating terminals were situated just below the right and left septal endocardial surface. Bipolar complexes were recorded between consecutive terminals of the stimulating needle. Propagation of these driven beats along the needle electrode occurred smoothly and continuously with a mean velocity of 46.4 cm/sec and a standard deviation of 2.7 cm/sec, both in an epi-endocardial direction and vice versa. Mean velocity of the stimulated impulses through the interventricular septum was from left to right 44.9 cm/sec, and from right to left 43.4 cm/sec. Activity in the septum elicited by stimuli applied both at the right and left surface progressed smoothly without local delays.

Conduction velocity in the specialized conducting system was not measured directly because this would have necessitated exploration of the septal surface under direct visual control.

In one heart, two Purkinje spikes were recorded in the subendocardial layer of the anterior left septal surface, which is presumably supplied by the fasciculus anterior. They were located at a distance of about 2 cm and the time interval was 10 msec, indicating that conduction velocity may be of the order of 2 m/sec, which agrees well with findings in the dog's heart.⁵

Atrial Excitation

In two hearts extensive exploration of atrial excitation could be performed. It was difficult to locate exactly the sino-atrial node. Early activity started in a relatively large area next to the right border of the superior caval vein. The spread of excitation over the atrial surface occurred according to more or less concentric isochrones. A more rapid progress of the activity occurred in the region of the taenia terminalis. In one heart, there was also a displacement of the isochrones on the crest of the interatrial band zone; in the other heart no such displacement was found in this region (fig. 5). The latest part to be activated was the left atrial appendage. A few recordings at sites near the left inferior pulmonary veins indicate that this region is activated as late as the left atrial appendage during normal sinus rhythm; the data are too few to be represented in the illustrations.

In one heart, atrial excitation during regular driving of the ventricles at a substantially higher rate than the sinus rhythm was explored. Retrograde V-A conduction was present, so that we may speak of atrial activation during a simulated nodal rhythm.

Earliest epicardial breakthrough occurred at the part of the right atrium between the inferior caval vein and the A-V sulcus. A second early area, activated 25 to 30 msec later, was found at the junction of right and left atrium, near the right wall of the aorta (fig. 5 D).

Control Experiments in Dogs' Hearts

These experiments were performed to compare the pattern of ventricular excitation in situ with that during perfusion of the isolated heart. The polarity of the bipolar complex indicates the direction of the spread of excitation: when activity spreads from endocardium to epicardium, the complex is positive; when inward spread is present, the complex is negative. Bipolar complexes recorded between consecutive intramural terminals showed the same polarity before and after isolation of the heart, indicating that the excitation front passed the needle electrodes in the same way in the in situ heart and in the

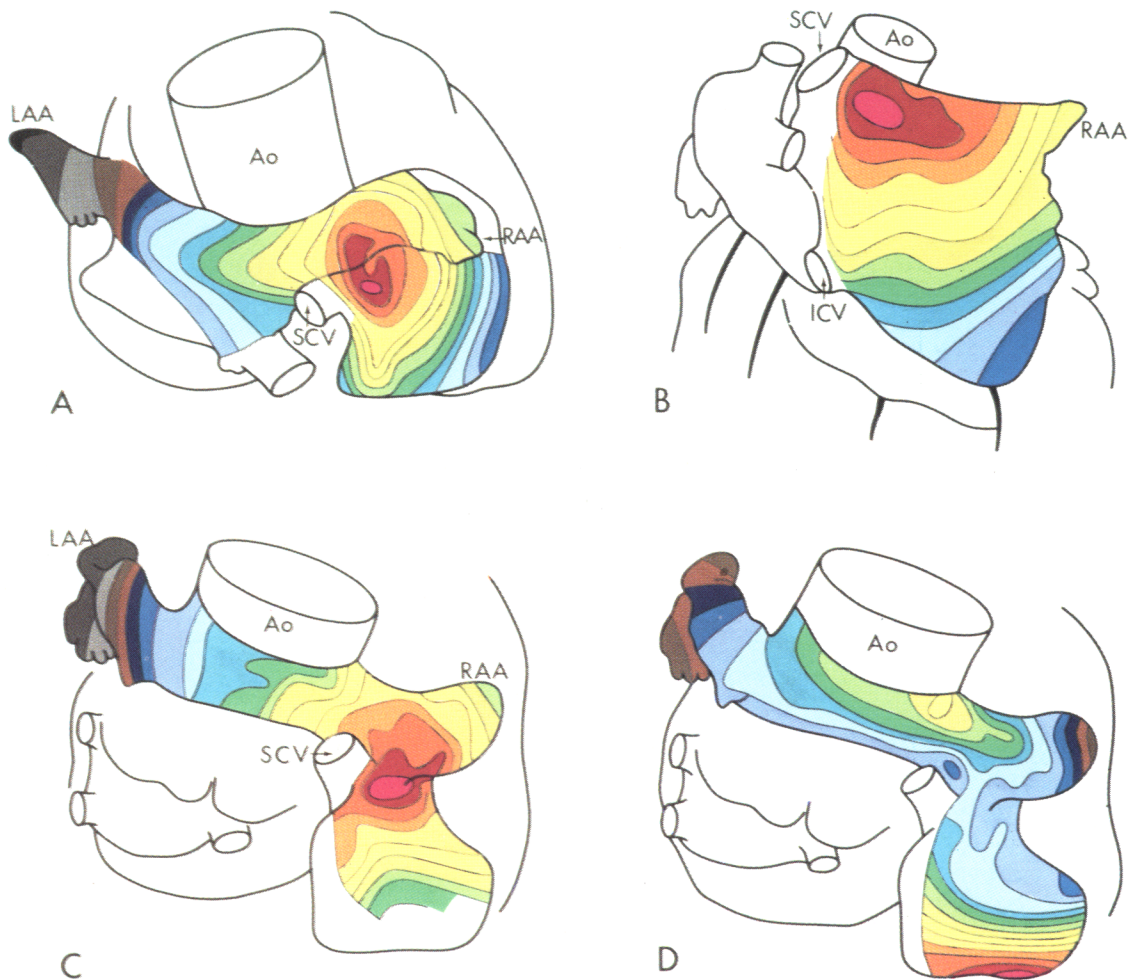
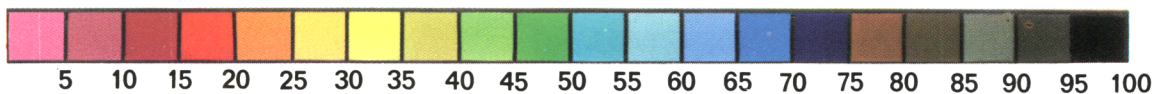


Figure 5

Isochronic representation of the atrial activation of two human hearts. Color scheme is the same as in figure 1, except that the earliest activity on the atrial surface (with respect to the activity at a fixed reference electrode on the right atrial appendage) was taken as zero time. A and B show different aspects of the same heart during sinus rhythm; A is a superior view of part of the right atrium and the interatrial band zone; the right atrial appendage is folded outward; B is a posterior view of the right atrium.

C and D show the activation pattern of the interatrial band zone and right atrial surface of another heart during sinus rhythm (C), and during retrograde (V-A) conduction when stimulating the ventricle (D). Ao = root of the aorta; LAA = left atrial appendage; RAA = right atrial appendage; SCV = superior caval vein; ICV = inferior caval vein.



isolated heart. The voltage of the bipolar complexes decreased to about one third of the original value after isolation.

The pattern of ventricular excitation, as judged from isochrone maps of sections of the hearts, did not change after isolation. However, total excitation was completed earlier in the isolated heart, the difference being in the order of 20%. Diagrams indicating the time of arrival of the excitatory wave at each terminal of the different multi-electrode needles consistently demonstrated that the same terminals were activated earlier in the isolated heart than in the in situ heart, while the overall sequence of excitation remained the same.

By giving a premature stimulus at the subepicardial terminal and measuring the time of arrival of the activation front at the other terminals of the same multi-electrode, an estimate was made of the conduction velocity in the in situ heart and in the isolated heart. The data were expressed as the time needed to bridge the interterminal distance of 2 mm, and these values were compared for the in situ heart and the isolated heart. The activation front crossed the 2-mm interterminal distance faster in the isolated heart than in the in situ heart. The differences were highly significant in the three hearts, P being <0.0001 , ≤ 0.0014 , and <0.0001 , respectively. The average conduction velocity in situ was 40.3 cm/sec, 36.1 cm/sec, and 35.5 cm/sec, respectively. In the isolated heart these values were 62.7 cm/sec, 56.3 cm/sec, and 50.1 cm/sec. The changes occurred within 30 minutes after isolation of the heart; thereafter the situation remained stable during the next 3 hours.

Discussion

Validity of Methods

It is evident that total excitation studies of isolated hearts have many pitfalls. The removal of the heart about half an hour after death and the perfusion methods may give rise to great changes in excitation pattern. In control experiments in canine hearts, in which the procedure of removal of the human heart was simulated as closely as possible, the in situ excitation of the heart was compared with excitation during perfusion. The general pat-

tern of excitation did not change after isolation of the heart. However, total excitation in the perfused heart was completed earlier than in the in situ heart. Also, conduction velocity, determined by stimulating the heart at subepicardial terminals both in situ and during perfusion, increased upon isolation. We are unable to explain why isolation of the heart leads to an increase in conduction velocity. We are also unable to explain why isolation of the heart produces a reduction in the voltage of complexes. Measurements in the normal human heart, performed during surgical interventions, indicate a conduction velocity of about 30 cm/sec.⁶ In the isolated perfused human heart we found a conduction velocity in the order of 45 cm/sec. Thus, it would seem as though the process of activation proceeds more rapidly in the isolated human heart than in the heart in situ. The QRS duration of the hearts we studied varied from 0.07 to 0.08 sec, as determined from electrocardiograms taken about 1 to 2 hours before death. Since the conduction velocity is higher in the isolated heart than in the in situ heart, one would expect the latest parts to be activated long before 70 or 80 msec. However, in the different hearts the latest moments of activation were: 71 msec (QRS, 0.08 sec), 62 msec (QRS, 0.07 sec), 65 msec (QRS, 0.07 sec), 80 msec (QRS, 0.08 sec), and 74 msec (QRS, 0.08 sec). Thus, the discrepancy between QRS duration in situ and the time required for total excitation in the perfused heart is much smaller than expected.

We considered the possibility of a time lag between the beginning of ventricular depolarization as judged from the departure of the left cavity potential from its base line in a high gain recording, and the beginning of the QRS in a standard lead. This time lag is certainly present when one uses an ECG lead in which the first part of the QRS complex is isoelectric. However, we made a few simultaneous recordings of several ECG leads together with intracavitary leads during routine cardiac catheterization and found that the earliest deflection in the peripheral ECG more or less

coincides with the beginning of the right or left intracavitary potential. It is also possible that the latest parts of the heart to be activated are so small as to contribute but little to the peripheral QRS complex. Indeed, even the longest QRS measured in limb leads is shorter than the duration of total depolarization as measured in vectorcardiograms.⁷ Thus, the total excitation time may appear to be considerably longer than the QRS, and this effect would offset the increase in conduction velocity during perfusion.

Epicardial Excitation

Most authors agree that the earliest epicardial breakthrough in the human heart occurs at the area pretrabecularis of the right ventricle,^{6, 8, 9-11} and that the pulmonary conus is activated late.^{6, 10, 11} The few data available about the activation of the posterior basal region of the right ventricle indicate that this area is activated late.⁹⁻¹¹ Data concerning the epicardial activation pattern of the left ventricle are in less agreement. Early activation has been reported to occur at the anterolateral surface near the left atrial appendage,¹² at any level paraseptally,¹¹ at anterior and posterior paraseptal zones,^{8, 13} at the posterior part of the apex,¹⁰⁻¹² and at the left paraseptal zone.¹⁰ The last activated areas of the left ventricle are said to be the posterobasal area,^{6, 9, 10, 12} the lateral half of the anterior surface and lateral surface,¹¹ and the upper portion of the left border.⁸ It should be emphasized that small areas of early epicardial activation can easily be missed when only a limited number of locations is explored. This is also apparent in our study: In the two hearts where recordings from only about 50 epicardial sites have been made (fig. 4C and F), the early epicardial breakthrough areas found in other hearts are missing. Another consequence of a greater accuracy of epicardial mapping due to sampling more points is that the isochronic lines become more irregular. This is not surprising since the activation front does not actually spread over the epicardial surface, but excitation spreads from endocardium to epicardium. Slight variations in wall thickness may account for

differences in epicardial activation in closely adjacent areas. In general, the epicardial activation pattern reflects the excitation of the inner layers of the heart muscle. Thus, the sites of early epicardial breakthrough correspond to early activated endocardial regions: the area pretrabecularis of the right ventricle, the left anterior basal and middle paraseptal regions, and the left midposterior paraseptal region. The small area activated early on the epicardium near the apex which was sometimes found does not appear to correspond particularly to an early activated endocardial region but probably results from early activity in the lower posterior wall. It should be stated here that our data from intramural sites close to the apex are scant.

Intramural Excitation

Studies in canine hearts show that earliest activity occurs in a central area on the left septal surface.^{3, 10, 14-19} The septal vector, being directed from left to right, and also from apex to base and from front to back,^{18, 19} would be responsible for the earliest deflections in the QRS complex.^{3, 15} From several studies, however, it emerges that early activity on the left septal surface is nearly simultaneous with activity in the free wall of the left ventricle,^{14, 17} and it has been stated that the mean septal vector could be negated by the simultaneously occurring activity in the free wall.²⁰ Our data show that in the human heart excitation of the endocardial surface starts synchronously at three widely different locations. One, in the anterior basal wall of the left ventricle near the aortic root, is probably excited by an offshoot of the anterior fasciculus of the left bundle branch. The remainder of the anterior fasciculus probably distributes excitation to the area in the midseptum, while the posterior fasciculus provides the area in the lower third at the junction of septum and posterior wall. Thus, the initial deflection in left precordial leads is affected by (1) septal excitation proceeding to the right, (2) excitation in the upper part of the anterior wall of the left ventricle proceeding toward the exploring electrode, and (3) excitation in the posterior wall moving in the opposite direc-

tion. Five to ten milliseconds later, excitation proceeds through the free wall of the right ventricle and moves from right to left in the mid-anterior part of the septum. Data available from canine heart studies agree that earliest activity on the right septal surface is always later than on the left side.¹⁷⁻¹⁹ At this point it should be stated that we have no information about the activation of the papillary muscles. Since the papillary muscles are in close proximity to the earliest activated areas, it may be assumed that activity in the papillary muscles contributes in an unknown manner to the vector of earliest activity.

Atrial Activation

In the two hearts in which atrial excitation was explored, activity spreads more or less according to concentric isochronic lines over the atrial surface. In one heart (fig. 5A) there is a displacement of the isochrones in the interatrial band. This might suggest a higher conduction velocity along the crest of the interatrial band, that is, along Bachmann's bundle. However, the widths of the isochronic areas both on the crest of the interatrial band and next to it are the same, and no increase in the width of the isochronic area is apparent as activity proceeds along Bachmann's bundle. The activity in this area was mapped according to measurements at 50 different electrode terminals which were situated more or less parallel with the direction of the spread of activation. Activity proceeded from one terminal to the other at the same velocity of about 1 m/sec on the crest of the interatrial band and next to it. The displacement of the isochrones seems due only to the fact that activity reaches the midpart of the interatrial band earlier than the zones next to it. In the other heart no displacement of the isochrones in this area was observed. Our results are in disagreement with the findings of Wagner and associates²¹ who found in the canine heart a conduction velocity of 1.3 m/sec on the crest of the interatrial band and of 0.9 m/sec in a pathway parallel with and below the crest.

Puech and associates²² considered the problem concerning specialized pathways in the atrium unsolved. They found that the impulse

"travelled with extreme ease along the intercaval and interauricular band zones." Our findings do not point in the direction of a specialized pathway of conduction along which activity spreads preferentially from the right to the left atrium. A more meticulous mapping might reveal slight differences in conduction velocity along certain areas of the interatrial band, but this might solely be due to the arrangement of the muscle fibers, conduction velocity being greater in those areas where the muscle is thicker. Indeed, this is probably the explanation for the slight preferential conduction found in the region of the taenia terminalis. Van der Kooi and co-workers²³ stated that the atrial activity in dogs' hearts spreads radially over the atrial surface but is more or less deviated in the course of thicker muscle ridges in the atrial wall. Of course we are not in a position to make statements about fibers specialized in other respects, as for instance resistance to K intoxication.²¹

Acknowledgment

The authors are greatly indebted to Professor Dr. W. Noordenbos and Dr. A. J. M. van der Werf for their help and cooperation, essential for this study. The authors wish to express their thanks to Drs. E. J. Müller and V. Manger Cats, and to all members of the department for their enthusiastic help in all stages of this investigation. Thanks are due to Hoechst-Holland N. V., Amsterdam, which provided us with demineralized Haemacel.

References

1. BODEN E, NEUKIRCH P: Elektrokardiographische Studien am isolierten Säugetier- und Menschenherzen bei direkter und indirekter Ableitung. *Pflüger Arch Ges Physiol* 171: 146, 1918
2. KOUNTZ WB, PRINZMETAL M, PEARSON EF, ET AL: The effect of position of the heart on the electrocardiogram: I. The electrocardiogram in revived perfused human hearts in normal position. *Amer Heart J* 10: 605, 1935
3. SCHER AM: Newer data on myocardial excitation. In *Electrophysiology of the Heart*. Edited by B Taccardi, G Marchetti. New York, Pergamon Press, 1965
4. DURRER D: Experimenteel onderzoek naar het verloop van het activatieproces in de hartspier. Amsterdam, Scheltema & Holkema, 1952
5. WEIDMANN S: Effect of current flow on the membrane potential of cardiac muscle. *J Physiol* 115: 227, 1951

6. DURRER D: Electrical aspects of human cardiac activity: A clinical physiological approach to excitation and stimulation. *Cardiovasc Res* 2: 1, 1968
7. SIMONSON E: Differentiations between normal and abnormal in electrocardiography. St. Louis, The C. V. Mosby Company, 1961, p 67
8. JOUVE A, CORRIOL J, TORRESANI J, ET AL: Epicardial leads in man. *Amer Heart J* 59: 856, 1960
9. DURRER D, BÜLLER J, GRAAFF P, ET AL: Epicardial excitation pattern as observed in the isolated revived and perfused fetal human heart. *Circulation Research* 9: 29, 1961
10. DURRER D, ROOS JP, BÜLLER J: The spread of excitation in canine and human hearts. In *Electrophysiology of the Heart*. Edited by B Taccardi, G Marchetti. New York, Pergamon Press, 1965
11. BARBATO E, PILEGGI F, DEBES AC, ET AL: Study of the sequence of ventricular activation and the QRS complex of the normal human heart using direct epicardial leads. *Amer Heart J* 55: 867, 1958
12. BARKER PS, MACLEOD AG, ALEXANDER J: The excitatory process observed in the exposed human heart. *Amer Heart J* 5: 720, 1930
13. JOUVE A, HENRY E, CORRIOL J, ET AL: Les dérivations épicaudiales chez l'homme. *Arch Mal Coeur* 51: 626, 1958
14. BOINEAU JP, HILL JD, SPACH MS, ET AL: Basis of the electrocardiogram in right ventricular hypertrophy. *Amer Heart J* 76: 605, 1968
15. SCHER AM, YOUNG AC: Ventricular depolarization and the genesis of QRS. *Ann NY Acad Sci* 65: 768, 1956-1957
16. VENEROSE RS, SEIDENSTEIN M, STUCKEY JH, ET AL: Activation of subendocardial Purkinje fibers and muscle fibers of the left septal surface before and after left bundle branch block. *Amer Heart J* 63: 346, 1962
17. SCHER AM, YOUNG AC, MALMGREN AL, ET AL: Activation of the interventricular septum. *Circulation Research* 3: 56, 1955
18. BURCHELL HB, ESSEX HE, PRUITT RD: Studies on the spread of excitation through the ventricular myocardium: II. The ventricular septum. *Circulation* 6: 161, 1952
19. SODI-PALLARES D, RODRIQUEZ MJ, CHAIT LO, ET AL: The activation of the interventricular septum. *Amer Heart J* 41: 569, 1951
20. BURCHELL HB: Current problems of excitation. *Ann NY Acad Sci* 65: 741, 1956-1957
21. WAGNER ML, LAZZARA R, WEISS RM, ET AL: Specialized conducting fibers in the interatrial band. *Circulation Research* 18: 502, 1966
22. PUECH P, ESCLAVISSAT M, SODI-PALLARES D, ET AL: Normal auricular activation in the dog's heart. *Amer Heart J* 47: 174, 1954
23. VAN DER KOOI MW, DURRER D, VAN DAM R TH, ET AL: Electrical activity in sinus node and atrioventricular node. *Amer Heart J* 51: 684, 1956

