Asynchrony of recovery from the refractory state has been emphasized repeatedly as a major factor in the induction of ventricular fibrillation by strong stimuli applied during the "vulnerable" period. The role of asymmetry of refractoriness, excitability, and conduction has been appraised thoroughly by Brooks et al.1 Some of the postulates proposed in their discussion have been tested and supported by recent studies in this laboratory; a number of agencies which initiate or predispose to the induction of ventricular fibrillation were shown to increase the temporal dispersion of recovery from the refractory state.2-4

When an early premature response is evoked in an irregularly excitable field, its propagation from the site of origin must also be irregular, and the recovery of excitability from the premature response should be even more greatly dispersed. Increased temporal dispersion of the refractory period duration determined at numerous points close to the site of origin of early premature ventricular responses has been demonstrated.2

If vulnerability to fibrillation during the relatively refractory period is due to the non-uniform excitability of the tissue, then premature responses should be characterized by a lower fibrillation threshold and a longer duration of the vulnerable period. This possibility was tested long ago by Wégría, Moe, and Wiggers, who found that "... the vulnerable period of premature beats is extended nearly to the end of the isometric relaxation process, but ... the fibrillation threshold is not significantly altered." It was concluded: "Our results certainly fail to show that a greater degree of asynchronicity in termination of contractions in premature beats reduces the fibrillation threshold."

In the study by Wégría et al., premature beats were evoked by condenser discharges through one pair of electrodes, and the fibrillation threshold was estimated with d-c shocks applied through another pair at a different site. No systematic attempt was made to study the earliest possible premature beats. Because the temporal dispersion of recovery must be greater at the site of origin of the premature response than at a more distant point, and because asynchrony has been shown to be greater for very early premature responses than for later ones,2 possible reasons for the failure of the earlier study to confirm Wiggers' hypothesis become apparent. The present study was undertaken to examine these possibilities.

Methods

Mongrel dogs ranging in weight from 9 to 18 kg were anesthetized by intravenous injection of sodium pentobarbital, 35 mg/kg. Under artificial respiration, the chest was opened in the midline, and the heart was exposed and suspended in a pericardial cradle. To reduce variations in the level of autonomic nervous activity, the heart was denervated acutely by cutting both cervical vagi and extirpating the stellate and upper thoracic sympathetic ganglia on both sides. Most of the techniques employed in the present experiments have previously been described in detail.2,3

The stimulating and recording electrodes were small steel hooks with an interelectrode distance of 1 to 1.5 mm. A pair of stimulating electrodes was attached to the epicardial surface of the right ventricle. Five to eight pairs of recording electrodes were arranged at various distances up to 45 mm from the stimulating electrodes. A

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variable interval generator was used to drive two Tektronix pulse generators (A and B) which, in turn, delivered rectangular pulses of variable interval, duration, and strength through isolation transformers to the ventricles. After the S-A node had been inactivated by crushing, the ventricles were driven by stimuli (S1) of 2 msec duration at 1.5 times the diastolic threshold, and at a cycle length of 350 to 400 msec.

Electrograms recorded at various distances from the site of basic stimulation were displayed on an eight-trace oscilloscope and photographed on paper moving at 100 mm/sec. Conduction time was determined at various distances by measuring the delay between the basic stimulus (S1) and the first rapid deflection of responses (R1) recorded at various distances. This criterion is admittedly arbitrary, but the shape of the contours representing onset of excitation at various recording sites in the graphs of figure 1 and figure 3 would not be significantly changed if another criterion was used, e.g., the time of the first peak in polyphasic responses. Conduction time of an early premature response (R2) was also determined at various distances following a premature stimulus (S2) delivered through the same S1 electrodes, or through a different pair of electrodes at some distance from the site of basic stimulation.

The refractory period (RP) of the ventricle was assessed as the R1S2 interval at various distances from the site of basic stimulation. By observation of responses at high sweep speed on a dual beam oscilloscope, the time of the rapid deflection (R1) relative to the S1 artefact was determined at each recording site. The recording electrodes were then switched to pulse generator B which delivered a test stimulus of 2 msec duration at any desired interval after the basic stimulus from pulse generator A. The test stimulus

![Diagram of electrograms](image)

**Figure 1**

Electrograms on the left were recorded at 8 and 32 mm from the point of application of the basic (S1) and two early premature (S2 and S3) stimuli. The sequence of the responses (R1, R2 and R3) and their corresponding RPs (shaded areas) at various points is plotted on the right. RP in each case was estimated with test stimuli of 1.5 times threshold. Exp. 3-10-64.
amplitude was displayed on one beam of the oscilloscope by means of a Tektronix current probe amplifier. The temporal position of the test stimulus relative to the previously determined position of R1 at the test site was recorded.

In the manner described above, thresholds for excitation were measured at various intervals of the cardiac cycle at each pair of recording electrodes placed at various distances from the site of basic stimulation. The success or failure of the test stimulus in evoking propagated excitation was indicated by recording the response from reference electrodes placed somewhere else in the ventricle. When the RP was estimated at the site of the basic driving stimuli, the secondary wirings of the two pulse generators were connected in series, so that test stimuli of independent parameters could be applied through the same pair of electrodes. In some experiments, the refractory periods at various sites were estimated only with test stimuli of 1.5 times the diastolic threshold.

The fibrillation threshold of basic or premature responses was estimated at various distances from the stimulated site by means of rectangular pulses of 10 msec duration and up to 50 milliamperes, triggered by the basic or premature pulse generator. The vulnerable period was scanned at intervals of 10 msec by test shocks at four times the diastolic threshold. Scans were repeated at increasing stimulus intensities until fibrillation occurred. Thus in each case, and at each electrode site, the minimal fibrillation threshold was determined by a-c countershock, and 15 minutes were allowed for recovery before additional observations were made.

Results

ASYMMETRY NEAR STIMULATED SITE

In the study by Han and Moe, the temporal dispersion of recovery was estimated as the range of refractory periods (RPs) determined at 12 separate points within a radius of 4 mm from a central point of stimulation on the anterior surface of the right ventricle. In a series of six experiments the average dispersion was less than 20 msec following a basic driven response, but was nearly doubled following the earliest possible premature beat. Later premature beats, initiated at the same site as the basic driven responses, but after the expiration of the relatively refractory period (RRP), showed no significant increase in the range of RPs estimated at the 12 test sites.

These results suggest that the inherent asymmetry of the pattern of excitation and recovery is compounded for a premature response which is initiated in the RRP of a preceding response, but not for one which starts in a field which, being fully recovered, is in a more nearly uniform state of excitability.

The early premature response must be refracted irregularly by the surrounding field, moving slowly through relatively inexcitable fibers and more rapidly, but still at submaximal velocity, through adjacent tissue in a more advanced state of recovery. Slow propagation near the site of origin must provide time for more complete recovery of more remote areas, with the result that the wave front should eventually encounter fully recovered tissue. At sites remote from the point of origin of the premature response, the situation then becomes comparable to that for a basic response, i.e., the dispersion of recovery following the premature response should be no greater than for the basic one. These assumptions were tested in the experiments illustrated in figures 1 and 2.

Responses recorded from eight pairs of electrodes, placed at radii of 8 and 32 mm from a site of stimulation, are reproduced at the left of figure 1. The time of application of a series of three stimuli is indicated by the vertical lines, S1, S2, and S3. Propagation of the resulting responses (R1, R2, R3) to the eight recording sites is indicated by the filled circles in the chart at the right. Following the last of a series of 12 driven responses (R1), the RP was determined at each of the eight recording sites; these values are indicated by the open circles in the chart. Estimates of the RP following R2 (the earliest possible premature response initiated at the stimulated site) are plotted similarly.

The dispersion of excitation and recovery times was greater at the near points; the R2 response was recorded at one of these sites before the expiration of the RP of the first response at a neighboring site equidistant from the stimulus. The dispersion of excitation and recovery increased following the premature response. At the more distant sites, the response...
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Distance from the point of basic stimulation is plotted on the ordinates in mm, and temporal dispersion of excitation and recovery on the abscissae in msec. Temporal dispersion of the basic excitation and of the early premature excitation is plotted on the left side, and that of corresponding recovery is plotted on the right side of the figure. Average values in five experiments. Analysis of variance indicates that distance was a significant determinant of dispersion of both excitation and recovery at the level of P < 0.01. The difference between basic and premature responses is significant at the same level.

A related effect of distance from a primary site of stimulation is illustrated in figure 3. In this experiment six pairs of recording electrodes were arrayed in line with a pair of stimulating electrodes at the distances indicated at the left of the figure. The duration of the RP as estimated at each of the recording sites is indicated in the graph at the right by the open circles; the RRP is indicated by the shaded area. When a premature response, R₂, was initiated within the RRP of the basic response, R₁, and at the same site as R₁, its propagation was encumbered near its origin, but it had emerged into fully recovered tissue within a distance of 14 mm. Premature responses initiated at distances of 21 and 42 mm, but also within the RRP at these points, were of course delayed by relatively refractory muscle, but they had emerged into fully recovered tissue within a distance of 7 mm in each case (responses indicated as B and C).

pattern was more nearly uniform, and no significant further asymmetry was imposed by the premature response. In some experiments dispersion was measured at various distances from stimulating electrodes attached near the right ventricular apex, and repeated when the stimuli were shifted to the pulmonary conus. In each case the dispersion was greatest near the stimulated site.

The average results of five such experiments are plotted as bar graphs in figure 2. Dispersion of excitation for the basic response, nowhere very great, was higher within the radius of presumably intramuscular propagation (i.e., within 12 mm). The difference between the 0 to 6 mm and the 7 to 12 mm points may be due to the fact that tissue within a finite radius of the suprathreshold S₁ stimulus must be excited simultaneously. Dispersion of excitation for the premature response was higher than for the basic response at all sites. Dispersion of recovery was also greater within the 12 mm radius, and diminished at greater distances for both basic and premature responses. No significant difference was found between the values at 0 to 6 and at 7 to 12 mm for either basic or premature responses, but analysis of variance revealed a significant contribution of both distance and prematurity.

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As shown in the lower half of the figure, the propagation of a third response initiated at the primary site (A) was still further depressed; it did not encounter fully recovered tissue until it had traveled beyond 14 mm, nearly 100 msec after S3. The course of R3 responses initiated at distances of 21 and 42 mm (B and C, respectively), however, was not appreciably different from the comparable R2 responses. It follows that the field in which these remote responses were evoked following R2 was not significantly different from that following the basic R1 response.

**Fibrillation Threshold as a Function of Distance**

The increased asymmetry at or near the site of origin of a premature response should provide a field in which the likelihood of fractionation, re-entry, and fibrillation is also increased. The fibrillation threshold, in accord

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**FIGURE 3**

Electrograms in the left upper quadrant display activities at various distances in response to a premature stimulus (S2) applied at the same point as S1 in (A); at 21 mm in (B); and 42 mm in (C) from the point of application of S1. The time-distance plot in the right upper quadrant depicts conduction of the basic impulse (R1) and of premature impulses (R2) originating at the three different points. The shaded area represents RRP following R1. Electrograms in the left lower quadrant display activities at various distances in response to an additional premature stimulus (S2) delivered to three different points after S1 applied at the same point as S1. The plot in the right lower quadrant depicts conduction of the second premature impulse (R2) originating at three different points. The shaded area represents RRP following R2. Exp. 3-17-64.
with Wiggers' initial hypothesis, should be lowest where the degree of asymmetry is greatest.

The results of five experiments in which the fibrillation threshold was estimated at various distances from a stimulated site are summarized in figure 4. In all cases the driving and premature stimuli were introduced through the same pair of electrodes. The threshold current strength necessary to produce fibrillation, when applied during the vulnerable period of the basic response, is indicated by the open bars, and that for the earliest possible premature responses, by the stippled bars.

The fibrillation threshold for the basic response was lowest when the test stimulus was applied either through the same electrodes as the driving stimuli, or within a radius of 12 mm from them. Within this area the threshold was reduced by nearly one-half when the test stimulus was applied after the premature response. At the intermediate distances, the fibrillation threshold was reduced by about 35% for the premature response, but was significantly higher than for the near points. At distances of 25 mm or more from the stimulated focus, the threshold for the premature response was only slightly less than that of the basic response at the same sites. The effect of distance was the same whatever the site of the stimulated focus in the right ventricle.

Discussion

In the study reported by Wégria et al. several stimulation sequences were used to assess the vulnerability of premature beats. In one series of observations ventricular premature beats were evoked at various times following a normally propagated response of supraventricular origin. The premature responses were initiated by brief condenser discharges passed through one pair of electrodes; the test stimuli were d-c shocks of about 20 msec duration, keyed at appropriate intervals after the condenser discharges and delivered through a separate pair of electrodes attached to the left ventricular surface. In the other
series, the heart was driven by rhythmic induction shocks delivered to the right or left ventricle through a third pair of electrodes. No significant difference in the fibrillation threshold was observed between basic and premature beats in any of these conditions.*

The results of the present study indicate that the fibrillation threshold estimated close to the site of origin of a premature beat is decreased, provided that the premature response is closely coupled to the preceding basic response. The results thus confirm Wiggers' original hypothesis, and they provide an explanation for the failure of the earlier experimental test.

The temporal dispersion of recovery of normally propagated ventricular responses is significant but is usually not greater than 5 to 10% of the mean duration of the RP. At various points near the site of origin of an early premature beat the range of RPs is considerably increased; with asynchronous excitation those elements which are excited earliest are subjected to a greater abbreviation of RP than those which respond later to the premature stimulus. When a premature response is initiated after the expiration of the RRP, on the other hand, the fibers within the effective field of the stimulus will respond more nearly synchronously; all fibers will have experienced nearly the same preceding cycle length (R, R'), and there will be no significantly increased dispersion of recovery over that demonstrable for the basic cycle. As a result of slow conduction near the point of stimulation, re-excitation at some distance from the site of origin of the premature response will be delayed beyond the expiration of the RRP. The situation at remote sites, therefore, should not differ appreciably for basic and premature beats. In the experiments reported here the distance at which the effect of prematurity is dissipated appears to be about 12 to 15 mm from the stimulated site (fig. 3). Accordingly, the fibrillation threshold for basic and premature responses should not be greatly different at remote sites.

It was found that the degree of temporal dispersion of recovery for basic driven beats as well as for premature beats was greater within 12 mm of the site of the driving electrodes than at greater distances (fig. 2). Correspondingly, the fibrillation threshold was also significantly less (fig. 4). It has also been observed (Han, unpublished observations) that when the ventricles are driven by basic stimuli applied to the epicardial surface, the RP of the R1 response is significantly shorter at sites near the basic S1 electrodes than at more remote sites, although the cycle length (R1R1 interval) is, of course, the same at all points. This may have a bearing on the reduced fibrillation threshold, at sites near the origin of the basic response, but an explanation may be stated also in terms of the asymmetry of the tissue. When the ventricles are driven by stimuli applied to a point on the epicardial surface, the initial propagation of the basic responses through muscle occurs at a relatively slow velocity which is probably not uniform in all directions. As in the atria, conduction is probably more rapid in the direction of the longitudinal axis of the fibers. Some asymmetry of the surrounding field must be expected, and this asymmetry should extend throughout the volume of tissue which is activated through muscle conduction, i.e., for a radius of 10 to 15 mm. At more remote sites, far enough away to be activated over the specialized conducting network, neighboring fibers will be more nearly in phase. Dispersion, as tested by estimation of the RP at numerous points, should, therefore, be greater within the zone of muscle conduction than in areas beyond it, and the fibrillation threshold should be correspondingly lower.

**Summary**

The degree of temporal dispersion of recovery of excitability of premature ventricular responses, estimated as the range of local refractory periods at various points on the surface of the right ventricle, is greater within a radius of 10 to 15 mm from the stimulated site

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*Tests of statistical significance were not applied in these experiments; Dr. Wiggers believed that physiologically significant results required no statistical treatment.
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than at greater distances. The fibrillation threshold of early premature beats is significantly lower than that of responses initiated in fully excitable tissue. The effect of prematurity on the fibrillation threshold is greater at points near the site of origin of the premature response. The observed spatial and temporal relationships suggest that the fibrillation threshold is related inversely to the degree of asymmetry in the excitable field.

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Fibrillation Threshold of Premature Ventricular Responses
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