Electrotonic Interaction during Canine Ventricular Repolarization

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SUMMARY **Canine ventricular refractory periods were measured during test site drive, during drive of single ectopic sites, during fusion drive from two ectopic sites, and during fusion drive from an ectopic site and the test site. Refractory period duration was dependent on the driving modes employed. Refractory periods were 2.63 ± 0.73%, 3.42 ± 0.87%, 3.54 ± 1.00%, and 4.68 ± 1.36% (mean ± SD) shorter during drive of single ectopic sites 2, 4, 6, and 40–60 mm, respectively, from the test site than during test site drive. During fusion drive from two ectopic sites, refractory periods were an average of 2.44 ± 1.04 msec (mean ± SD) less than during drive from a single ectopic site ($P < 0.005$). When fusion of activation, induced by ectopic and test site drive, was located within 4 mm or less of the test site, refractory periods during fusion drive were also significantly shorter than during test site drive ($P < 0.05$). Refractory periods were as much as 10 msec shorter when fusion occurred within 1 mm of the test site than their durations during test site drive. The differences in refractory periods measured during various driving modes were most likely due to electrotonic interactions during ventricular repolarization and are explicable on the basis of the intracellular distribution of potentials to be expected with each driving mode.**

ALTERED action potential duration due to depolarizing or repolarizing pulses applied to Purkinje and ventricular muscle fibers during repolarization has been reported.[1-5] Mendez et al.[6] showed that differences in action potential duration in Purkinje and muscle fibers are reduced by electrotonic interaction during repolarization. Recently, Abildskov[7] found that refractory periods at a ventricular site were shortened when fusion of activation fronts occurred near that site and ascribed the finding to electrotonic interactions during repolarization of ventricular muscle fibers. All these reports indicate that electrotonic interaction is one of the factors affecting cardiac recovery properties.

During repolarization, the ventricular site at which that process begins can be expected to receive a depolarizing effect from surrounding tissue because of greater positivity of intracellular potentials at surrounding sites. To determine whether such a depolarizing effect occurs, refractory periods at a test site were measured while driving the test site itself and while driving other sites at various distances from it. Refractory periods during these driving modes were compared with each other and the differences analyzed in relation to the distance between the test and driving sites. The differences were also analyzed in relation to the direction of propagation of activation fronts along the longitudinal and transverse axes of the heart. In addition, fusion of activation fronts near test sites was produced and demonstrated to have a repolarizing effect on the test site. This effect was analyzed with respect to distance between the site of fusion and the test site. The depolarizing and repolarizing effects on refractory periods demonstrated in this study provide a quantitative measure of electrotonic effects during repolarization of ventricular muscle in the intact dog heart.

Methods

Twenty-seven adult mongrel dogs weighing 15–28 kg were anesthetized with intravenous pentobarbital (30 mg/kg, iv) combined with a slow intravenous drip of pentobarbital (15 mg/kg in 500 ml of 5% dextrose in water). Additional bolus injections of pentobarbital (3–4 mg/kg, iv) were given as needed to maintain deep anesthesia. Under artificial respiration, the heart was exposed by midsternal thoracotomy and suspendend in a pericardial cradle. The sinus node was crushed and the heart was paced at a rate of 150 beats/min with stimuli delivered to the right atrial appendage. The stellate ganglia were extirpated and vagus nerves cut to reduce autonomic nervous effects on refractory periods.

Two kinds of multiple electrodes with interpolar distances of 1 mm were used for intramural and epicardial observations. The intramural electrode was constructed under a dissecting microscope from a bundle of 10 silver wires, 0.127 mm in diameter. The wires were insulated except at their distal ends. The ends of the wires in the bundle were arranged so they were separated by 1 mm along the longitudinal axis of the electrode assembly. The electrode assembly was equipped with a small hook at the distal end of the longest wire to secure it in the myocardium. This electrode assembly was mounted in a 19-gauge needle and plunged into the anterior wall of the left ventricle tangential to the ventricu-

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Supported in part by Program Project Grant HL 13480 and Research Grant HL 12611 from the National Institutes of Health, and the Richard A. and Nora Eccles Harrison Fund for Cardiovascular Research.

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Received September 16, 1977; accepted for publication April 27, 1978.

lar surface and transverse to the longitudinal heart axis. The needle was then withdrawn, leaving the electrode assembly anchored in the myocardium by the hook. Electrode locations were determined by dissection following the experiments, and the depth of the electrode assembly was documented to be approximately midway between the endocardial and epicardial surfaces. The epicardial electrode assembly consisted of 19 silver wires, 0.58 mm in diameter, embedded in a molded epoxy resin disc. Tips of the wires formed two straight lines of equal length at right angles to each other at the end electrode of each line. The tips of the silver wires were trimmed level to the disc surface to provide a smooth contact with the epicardium. The electrode assembly was sutured to the anterior epicardial surface of the left ventricle in an area between the left anterior descending coronary artery and its diagonal branch. The axis of one line of electrodes was parallel to the longitudinal axis of the heart. A disc electrode of chlorided silver, 3.7 cm in diameter, was placed subcutaneously in a hind leg as an indifferent stimulating electrode. After either the intramural or epicardial electrode assembly had been placed, the open chest was covered with a cloth to minimize temperature changes in the thoracic cavity, and the heart was driven for 45–60 minutes before measurements were begun.

Refractory periods were measured during various driving modes. When the ventricle was driven at a single site other than the one at which refractory periods were being measured, the driving mode is referred to as ectopic drive. When both driving and test stimuli were applied to the refractory period test electrode, the driving mode is referred to as test site drive. When driving stimuli were applied to two ventricular sites simultaneously or separated by a varied interval, the driving mode is referred to as fusion drive. In some instances of fusion drive, one of the drive sites also was the test electrode site. In other instances of fusion, drive was from two sites other than the test electrode.

Drive and test stimuli were cathodal square waves of 1 or 2 msec duration from constant current sources unless otherwise specified. The intensity of the stimuli was 1.5 to 2 times diastolic threshold. The basic driving stimuli to various ventricular sites were applied simultaneously with those to the atrium in all experiments. Propagated responses to test stimuli were monitored on an oscilloscope using an ECG lead from electrodes on the neck and the left hind leg. Test stimuli were applied after every eighth basic driving stimulus and delayed in 1-msec increments until a propagated ventricular response occurred. During sets of observations, the driving modes were alternated and the average of 10 values measured during each driving mode was taken as the refractory period. An interval of at least 15 seconds was allowed to elapse between each measurement. The refractory period measured during test site drive was taken as the time of the earliest test stimulus which produced a ventricular response. Refractory periods during ectopic and fusion drives were obtained by subtracting activation time at the test site from the time of the earliest test stimulus which produced a response.

Activation time at the test site was taken as the average of 6 to 10 values measured from electrograms recorded before and after refractory period measurements. Activation time was determined from peak deflections of electrograms from the test electrode and another electrode 1 mm distant from it, or from intrinsic deflections in unipolar lead electrograms recorded from the test electrode and a Wilson central terminal. The location of fusion of activation fronts was determined from bipolar electrograms recorded prior to the measurement of refractory periods. The electrograms were recorded on a light beam oscillograph with a paper speed of 50 or 100 cm/sec. Observations were made to determine: (1) the effect of distance between driving and test sites on refractory periods, (2) the effects of fusion from two ectopic drive sites on refractory periods, and (3) the effects of fusion from ectopic and test site drive on refractory periods.

Effect of Distance between Driving and Test Sites

These observations were carried out in two ways. In one series, refractory periods were measured while driving from the test electrode and while driving from electrodes 2, 4, 6, and 40–60 mm away from the test electrode. The driving electrodes at 2–6 mm from the test electrode were on the epicardial multiple electrode assembly. The electrodes 40–60 mm away from the test electrode were constructed of insulated silver wire with a scraped segment and were placed on the right ventricular base.

In another series, refractory periods were measured at two test sites. Ectopic driving sites were at opposite ends of a straight line drawn through the test sites. Each ectopic driving site was 2 mm distant from one test site and 6 mm distant from the other. Refractory periods were measured during drive of each of the ectopic sites and during drive from the test sites themselves.

Effect of Fusion from Two Ectopic Sites

Refractory periods at a test site were measured during fusion drive from two ectopic sites, during drive from a single ectopic site, and while driving the test site. Fusion was produced by delivering stimuli to electrodes 8 mm to 5 cm apart. The test electrode was placed midway between the ectopic drive sites. In studies of epicardial refractory periods, the timing of the driving stimuli was adjusted so that activation fronts fused near the test site. Fusion of activation fronts was considered to be almost directly under the test electrode when QRS

spikes of two electrograms recorded from the test electrode site and electrodes on either side of it had opposite polarities, as shown in Figure 1. In studies of intramural refractory periods, the timing of the stimuli was adjusted by monitoring a bipolar electrogram recorded from the test electrode and an electrode 1 mm distal from it. The timing of stimuli was set so that the bipolar electrogram had a distorted configuration of small amplitude, indicating fusion of activation near the recording electrodes. An example is shown in Figure 2.

Activation times at epicardial test sites during ectopic and fusion drives were taken as the steepest downstroke of QRS spikes in unipolar electrograms from the test electrode. Only bipolar electrograms were recorded intramurally. The spike in the bipolar electrogram from the pair of electrodes that included the test site electrode was considered to represent the time activation was midway between the test site and the other pole of the electrode pair. The time of that spike was adjusted by a factor determined from the conduction velocity between the pairs of electrodes on the electrode assembly and the distance between the poles of the bipolar electrode that included the test site. This adjustment gave the activation time at the test electrode itself.

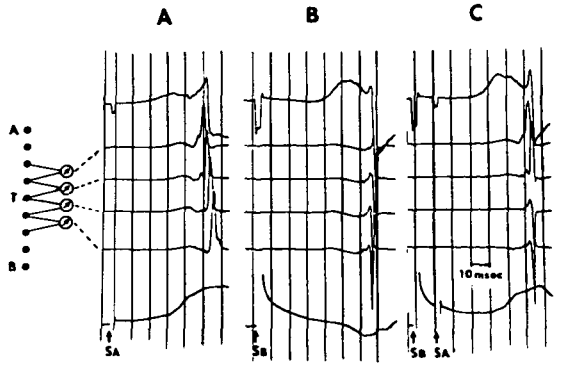

FIGURE 1 *Example of electrograms used to determine the site of fusion of activation fronts in epicardial experiments. The electrode configuration is shown schematically on the left. The interelectrode distances were 1 mm. Electrodes A and B were used for driving, and electrode T was used for refractory period testing. In each panel of recordings, the top trace is a unipolar electrogram recorded from the test electrode. The second through fourth traces are bipolar electrograms from the electrode sites indicated at the left of the figure. The bottom trace is a body surface ECG recorded from electrodes on the neck and left hind leg. In panels A and B, driving stimuli (SA and SB) were applied to electrodes A and B, respectively. The polarity and timing of QRS spikes show that the activation sequences along the electrode line were opposite during the two drives. As shown in panel C, when driving stimuli were applied to both electrodes A and B with SA delayed 12 msec after SB, the QRS spikes in the third and fourth traces had opposite polarities. QRS spikes of the third traces of panels A and C are similar to each other in polarity and shape, and those of the fourth traces of panels B and C are similar. This indicates that fusion of activation fronts occurred in the vicinity of the test electrode.*

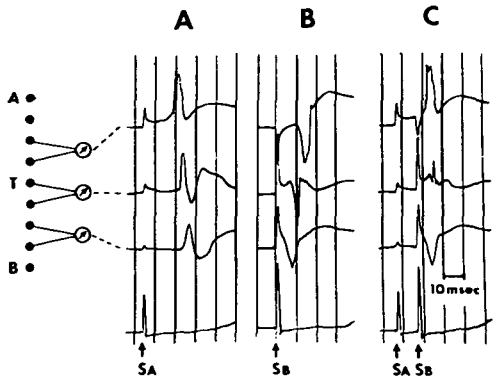

FIGURE 2 *Example of electrograms used to determine the site of fusion of activation in intramural experiments. Abbreviations in the figure are the same as in Figure 1. In each panel of recordings, the first three traces are bipolar electrograms recorded from electrode sites diagrammed on the left. The bottom traces are body surface ECGs recorded from electrodes on the neck and left hind leg. Recordings in panels A and B were obtained when driving stimuli were applied to electrodes A and B, respectively. The polarity of QRS spikes indicates the activation sequence along the electrode line was opposite during the two drives. Recordings in panel C were obtained while applying stimuli to both electrodes A and B with SB delayed 10 msec after SA. The small QRS spike in the tracing indicates fusion occurred between the test electrode and the adjacent electrode nearer B.*

Effects of Fusion from Ectopic and Test Site Drive

For these observations, an electrode at one end of the multiple electrode assembly was used as a driving electrode. An electrode at the other end was used for both driving and measuring refractory periods. The remaining eight electrodes were paired to record four bipolar electrograms which were used to determine the site of fusion. Electrograms were recorded during test site drive and ectopic drive as well as during fusion drive. The refractory periods at the driving site were measured while driving only the test site and during fusion of drives from the test and ectopic sites. With fusion drive, the timing of the stimuli was first adjusted so fusion occurred approximately midway between the two drive sites. Driving stimuli to the test electrode then were delayed by increments of 3 or 5 msec so fusion of activation occurred nearer the test electrode. The delay was not allowed to exceed the time of activation of the test site that occurred during ectopic drive. For each increment of delay between driving stimuli, electrograms were recorded and refractory periods measured.

Refractory periods were expressed as the mean value of 10 determinations ± the standard deviation, and data were analyzed with the paired *t*-test.

Results

Effect of Distance between Driving and Test Sites on Refractory Periods

To determine the distance over which activation sequence influenced recovery properties, time of recovery was measured during drive of an epicardial test site and during drive of sites 2, 4, and 6 mm away from the test site. Time of recovery was defined as the earliest time the test site could respond to a premature stimulus and included activation time from the ectopic drive sites. These recovery times would be expected to have a one-to-one relationship to activation time at the test site if activation sequence did not influence recovery properties. Figure 3 shows the results of 12 observations. A 45° line drawn from the origin of the plot shows the relation between activation and recovery times to be expected if there were no change in recovery properties due to distance between test and driving sites. When the driving site was close to the test site, time of recovery changed less than activation time. As the distance between drive and test sites was increased, the changes in recovery times and activation times followed each other. These findings indicate that recovery properties at a test site are influenced by activation initiated at sites near it, but activation initiated more than 4 to 6 mm away has little influence on recovery properties.

The graph in Figure 4 shows, as a function of distance between the test and driving sites, the percent by which refractory periods shortened during ectopic drive from the duration they had during test site drive. The percent shortening of refractory periods was greater as the distance between driving and test sites increased. Refractory periods were longest when the test sites themselves were driven. With two exceptions, refractory periods were shortest when sites 40–60 mm away from the test site were driven. Refractory periods were 4.4–13.4 msec shorter when the driving sites were 40–60 mm away from the test site than during test site drive.

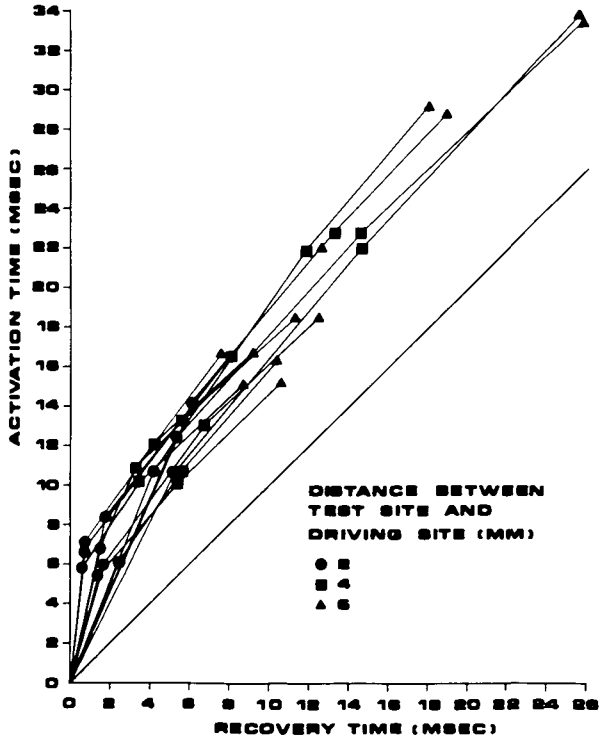

FIGURE 3 *Graph of the change in activation and recovery times of test sites when basic driving stimuli were 2, 4, and 6 mm from the test site. Activation and recovery times associated with test site drive are plotted at 0 msec. When the driving stimuli were within 2 mm of the test site, time of recovery changed less than time of activation. When the distance between driving and test sites was increased, the changes in times of activation and recovery followed each other.*

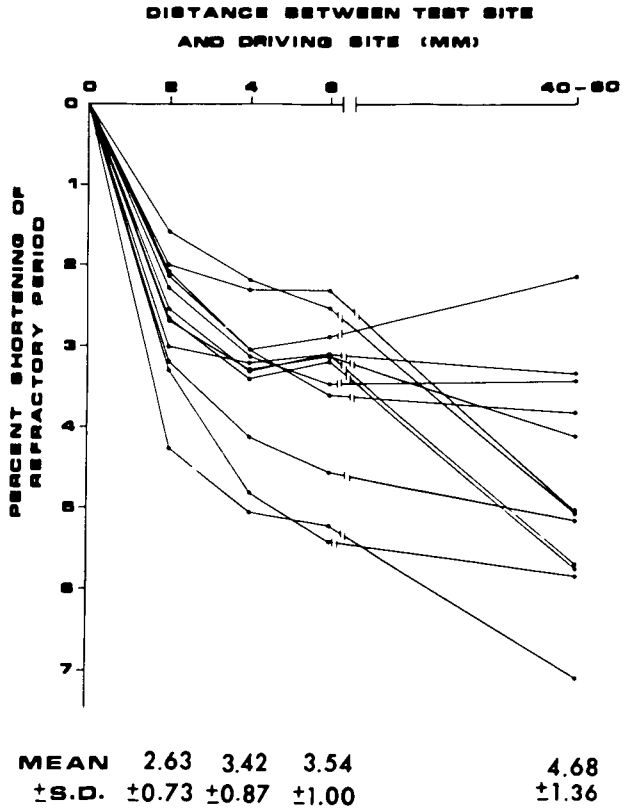

FIGURE 4 *Graph in which the percent shortening of refractory periods during ectopic drive from their durations during test site drive is plotted against the distance between the refractory period test site and the ectopic drive site. The mean values and standard deviations of percent shortening for each distance are indicated at the bottom of the graph. The percent shortening of refractory periods increased as the distance between driving and test sites was increased.*

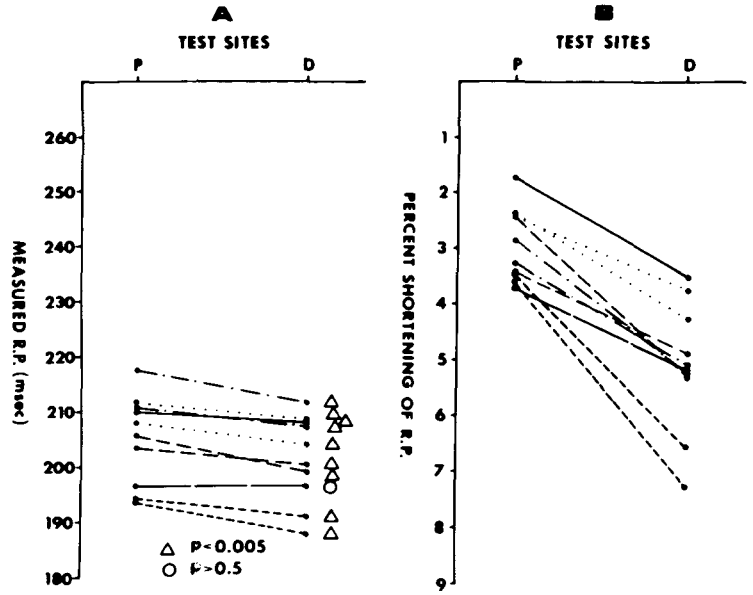

FIGURE 5 *A: Graph of epicardial refractory periods (R.P.) measured at two test sites 2 mm (P) and 6 mm (D) away from an ectopic driving site. The lines with the same symbols indicate pairs of observations made with two driving sites as well as two test sites. As indicated in the graph, the test sites 2 mm from the driving sites had significantly longer refractory periods than the test sites 6 mm from the driving sites in 9 of 10 observations. The P values for significance of differences are indicated in the figure. B: Graph of the percent shortening of epicardial refractory periods at test sites 2 and 6 mm from a driving site compared to the refractory periods measured at those sites when basic driving stimuli were also delivered to them. In all observations, the percent shortening was less at the test site 2 mm from the driving site than at the test site 6 mm from the driving site.*

In another set of observations, ectopic drive was initiated from electrodes situated 2 mm on either side of two test electrodes and in line with the test electrodes. The test electrodes were separated by 4 mm. Six observations were made during drive of one or the other of the ectopic sites. Four sets of observations, indicated by the lines with the same symbols in Figure 5, were made by driving first one and then the other of the ectopic drive sites. By switching drive sites in this way, the test electrode 2 mm distant from one drive site was 6 mm distant from the other drive site. These pairs of observations eliminated the possibility that differences in intrinsic recovery properties at the two test sites, rather than the effect of distance between drive and test sites, were responsible for the observed differences in refractory period. As shown in Figure 5A, in 9 of 10 trials with epicardial electrodes, refractory periods were significantly longer ($P < 0.005$) when the test site was 2 mm from the driving site than when the test site was 6 mm from the driving site. This finding was present despite alteration of the location of driving sites in the pairs of observations described above. The percent shortening of refractory periods during ectopic drive with respect to their values during test site drive was also determined. The percent shortening of refractory periods was less at the closer test site than at the more distant test site for all 10 of these observations of epicardial refractory periods (Fig. 5B). The average and standard deviation of percent shortening was 2.93 ± 0.67% when the test sites were 2 mm from

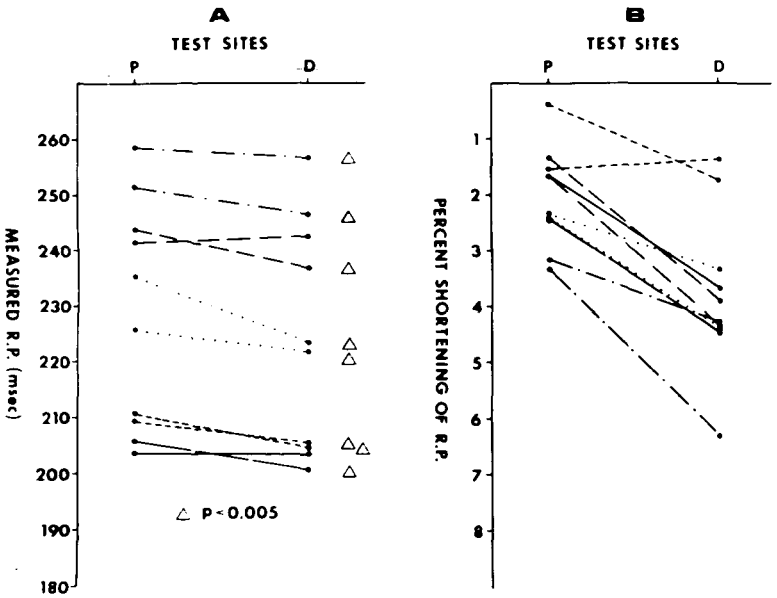

FIGURE 6 *A: Graph of intramural refractory periods at two test sites 2 mm (P) and 6 mm (D) away from an ectopic drive site. The lines with the same symbols indicate pairs of observations as described in the text. In 8 of 10 observations, refractory periods at test sites 2 mm away from the drive site were significantly longer than refractory periods at test sites 6 mm from the drive site. The Δ indicates significance of difference in the observations ($P < 0.005$). B: Graph of the percent shortening of intramural refractory periods at test sites 2 mm (P) and 6 mm (D) from an ectopic drive site from the refractory period duration measured when the basic drive was delivered to the test sites. In 9 of 10 observations, the percent shortening of refractory periods was less at the site 2 mm from the drive site than at the site 6 mm from the drive site.*

the drive sites and 5.06 ± 1.14% when the test sites were 6 mm from the drive sites ($P < 0.005$). These findings confirm the fact that, during ectopic drive, refractory periods shorten more at test sites distal from the drive site than at test sites near the drive site.

As shown in Figure 6A, refractory periods during ectopic drive were also significantly shorter at a distant than at a near test site ($P < 0.005$) in 8 of 10 series of observations of intramural refractory periods. In one series of observations, the refractory periods were slightly longer at the more distant site, and in one other observation there was no significant difference of refractory periods at the two test sites. In three of four pairs of observations, with alternation of the ectopic driving sites as described above, refractory periods at the closer test site were longer than those at the more distant site during both ectopic drives. The percent shortening of intramural refractory periods during ectopic drives from their durations during test site drive is shown in Figure 6B. There was less shortening at test sites 2 mm from the drive sites than at those 6 mm from the drive sites in 9 of 10 series of observations of intramural refractory periods. The average and standard deviation of the percent shortening in this series of observations was 2.03 ± 0.89% at the test sites 2 mm from the drive sites and 3.82 ± 1.43% at test sites 6 mm from the drive sites ($P < 0.005$). Thus, distance between driving and test sites had the same effect on intramural refractory periods that it had on epicardial refractory periods.

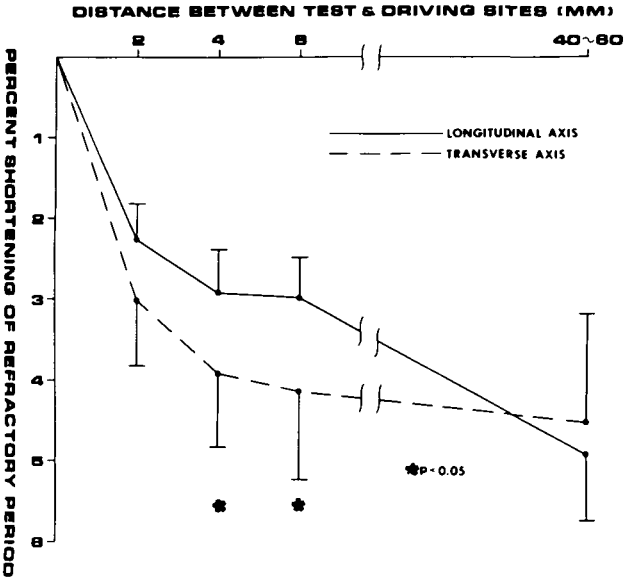

FIGURE 7 *Graph of the percent shortening of refractory periods at test sites during ectopic drive of sites 2, 4, 6, and 40–60 mm away from them in comparison to refractory period durations measured during test site drive. Data obtained with electrodes aligned on the longitudinal axis of the heart are shown with the solid line and data obtained with the electrodes aligned on the transverse axis are shown with the broken line. As indicated in the figure, there is significantly more shortening of refractory periods along the transverse than along the longitudinal axis during ectopic drive of sites 4 and 6 mm from the test site. There was no significant difference in the percent shortening along the two axes when sites 2 mm or 40–60 mm from the test site were driven.*

The effects of distances of 2 and 6 mm between driving and test sites on epicardial refractory periods were also analyzed with respect to the anatomic cardiac axis along which the sites were located. Nine observations were made with the electrodes parallel to the longitudinal axis of the heart and 13 observations were made with the electrodes perpendicular to the longitudinal axis. Along the transverse axis of the heart, when a site 2 mm from the test site was driven, refractory periods shortened 3.15 ± 0.62% from the durations measured during test site drive. Along the longitudinal axis, refractory periods shortened significantly less, 2.23 ± 0.40% ($P < 0.005$). When a site 6 mm from the test site was driven, refractory periods along the longitudinal axis also shortened significantly less 3.25 ± 0.60% than along the transverse axis 4.91 ± 1.21% ($P < 0.005$). The same analysis was performed on data illustrated in Figures 3 and 4. When sites 4 and 6 mm away from the test site were driven, the percent shortening of refractory period was significantly greater along the transverse than along the longitudinal axis (Fig. 7). However, when sites 40–60 mm away from the test site were driven, differences in the percent shortening of refractory periods on the two axes were not significant.

Effect of Fusion from Two Ectopic Drive Sites

Refractory periods of epicardial test sites measured during single ectopic drive, test site drive, and fusion drive from two ectopic sites are shown in Table 1. Refractory periods measured during fusion drive were significantly shorter ($P < 0.005$) than those measured during drive from a single ectopic site. Refractory periods were an average of 2.44 ± 1.04 msec less during fusion drive than during drive from a single ectopic site. In four of seven series of observations of intramural refractory periods, refractory periods during fusion drive were also significantly shorter than those during ectopic drive (Table 2). In the other three observations, there were no significant differences of refractory periods during these driving modes. The epicardial and intramural refractory periods were significantly longer ($P < 0.005$) during test site drive than those during ectopic drive in all observations (Tables 1 and 2).

Effect of Fusion from Ectopic and Test Site Drive

The effect of location of fusion due to drive of a test site and an ectopic site on refractory periods at the test site was also analyzed, and the results are

TABLE 1 *Refractory Period (RP) Change in Epicardial Experiments*

Experiment no.	Mean ± SD of RPs at test site				Difference of mean RPs			
	Ectopic drive (A)	Ectopic drive (B)	Fusion drive	Test site drive	A-B	Fusion drive-A E_A drive	Fusion drive-B E_B drive	Test site drive-A
1	178.10 ± 0.87	179.90 ± 1.04	177.50 ± 0.56	187.90 ± 0.88	−1.80*	−0.60*	−2.40*	9.80*
2	186.20 ± 0.72	187.60 ± 0.81	184.60 ± 0.70	191.80 ± 0.42	−1.40*	−1.60*	−3.00*	5.60*
3	189.20 ± 0.96	189.20 ± 0.87	186.50 ± 0.70	198.50 ± 0.71	0.00	−2.70*	−2.70*	9.30*
4	190.40 ± 0.51	191.90 ± 0.80	189.20 ± 0.64	197.60 ± 0.70	−1.50*	−1.20*	−2.70*	7.20*
5	201.10 ± 0.84	202.20 ± 0.79	199.90 ± 0.75	212.80 ± 0.63	−1.10	−1.20*	−2.20*	11.70*
6	203.30 ± 0.87	204.30 ± 0.76	201.60 ± 0.88	214.40 ± 0.52	−1.00	−1.70*	−2.70*	11.10*
7	210.80 ± 0.53	210.80 ± 0.07	208.40 ± 0.54	217.00 ± 0.00	0.00	−2.40*	−2.40*	6.20*
8	201.70 ± 0.96	204.70 ± 0.75	200.30 ± 0.71	214.80 ± 0.63	−3.00*	−1.40*	−4.40*	13.10*
9	186.60 ± 1.39	189.00 ± 1.20	184.30 ± 1.40	198.90 ± 1.20	−2.40*	−2.30*	−4.70*	12.30*
10	185.10 ± 0.70	186.00 ± 1.00	182.50 ± 0.83	201.20 ± 0.92	−0.90	−2.60*	−3.50*	16.10*
11	197.30 ± 0.58	194.50 ± 0.84	192.80 ± 1.12	205.80 ± 0.42	2.80*	−4.50*	−1.70*	8.50*
12	198.20 ± 0.68	198.70 ± 0.83	196.50 ± 0.80	205.40 ± 0.70	−0.50	−1.70*	−2.20*	7.20*

* $P < 0.005$.

shown in Figure 8. The shortening of refractory periods measured during fusion compared to refractory period durations measured during test site drive was significantly more when the site of fusion was within 4 mm or less of the driving site ($P < 0.05$). The shortening was greater when the site of fusion occurred closer to the driving site, and when fusion occurred within 1 mm of the test site, refractory periods shortened as much as 10 msec.

Discussion

Weidmann[1] reported that repolarizing pulses applied during repolarization shortened action potential duration in Purkinje fibers. Cranefield and Hoffman[2] reported that depolarizing pulses applied during repolarization prolonged the action potential durations of papillary muscle and repolarizing pulses shortened them. Vassalle[3] found that action potentials from Purkinje fibers could be terminated by anodal currents applied during the plateau phase. Kass and Tsien,[4] on the other hand, found that short depolarizing pulses accelerated repolarization of Purkinje fibers. They suggested that the increase in plateau amplitude induced by the depolarizing pulse accelerated time- and voltage-dependent current changes which trigger repolarization. Bassingthwaighte et al.[5] reported a similar study on sheep and calf ventricular muscle. They found that, in perfusion baths with 0.36 mM/Ca^{2+}, ventricular muscle action potential durations were prolonged when a constant current pulse was applied to the upstroke. Short duration pulses were used in the studies by these investigators, and the results may not be directly related to ours. However, the previous reports do suggest that electrotonic effects can influence action potential duration. In addition, Mendez et al.[6] showed that action potential durations of cells at the transitional zone between Purkinje and muscle fibers were electrotonically affected by differences of action potential durations at these sites. Abbreviation of action potential duration at a site proximal to conduction block induced by anodal current has also been reported.[8]

Repolarization begins at the same ventricular site at which excitation begins. The process is also completed earliest at that site provided differences in intrinsic action potential durations at that site and other ventricular sites do not exceed differences in conduction times between them. In experiments in which intramural and epicardial ventricular potential distributions were mapped, Spach et al.[9, 10] showed that repolarization began at ectopic driving sites. Under such conditions, myocardial sites surrounding the driving site would have less negative intracellular potentials than the driving site. In contrast, if the same site was affected by an acti-

TABLE 2 *Refractory Period (RP) Change in Intramural Experiments*

Experiment no.	Mean ± SD of refractory periods			Difference of mean RPs	
	Ectopic drive	Fusion drive	Test site drive	Fusion drive-ectopic drive	Test site drive-ectopic drive
1	220.80 ± 0.67	221.50 ± 1.07	229.10 ± 1.20	−1.30	6.30*
2	219.80 ± 1.03	219.30 ± 0.67	225.40 ± 0.52	−0.50	5.60*
3	200.40 ± 0.52	196.50 ± 0.79	210.30 ± 0.48	−3.90*	9.90*
4	185.40 ± 2.00	182.10 ± 1.89	190.30 ± 2.36	−3.30*	4.90*
5	235.00 ± 1.25	230.90 ± 1.06	238.40 ± 0.97	−4.10*	3.40*
6	199.60 ± 0.92	199.80 ± 1.05	206.90 ± 0.99	0.20	7.30*
7	225.20 ± 1.23	219.30 ± 1.18	228.80 ± 0.92	−5.90*	3.60*

* $P < 0.005$.

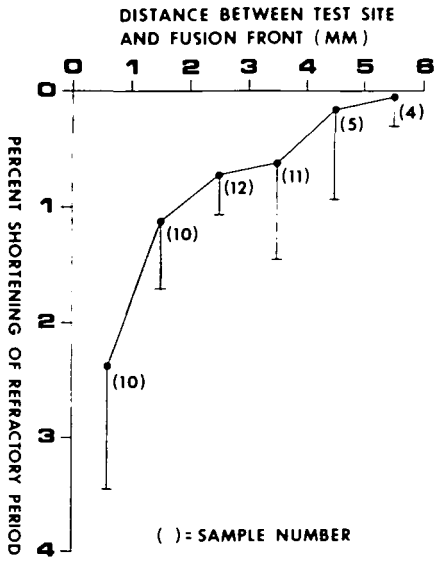

FIGURE 8 *Graph in which the percent shortening of refractory periods during fusion drive from the test and ectopic sites compared to the values measured during test site drive are plotted against the distance between the site of fusion and the test site. As the site of fusion of activation was located closer to the test site, there was a higher percent shortening of refractory periods.*

vation front propagating from a distance, the site would be surrounded by more negative potentials on one side and by less negative potentials on the other side. Thus, the site would be expected to receive a depolarizing effect from surrounding sites and have longer action potentials when it was driven than when it was affected by an activation front propagating toward it. At sites in close proximity to a driving site and within the range of electrotonic interactions, intracellular potentials would be affected by both depolarizing and repolarizing currents. Therefore, less prolongation of action potentials would be expected at these sites than at the driving site. As the test site is moved further from the driving site, the test site would be expected to receive a more marked repolarizing effect with less prolongation of refractory periods compared to those measured during test site drive.

In our experiments, refractory periods measured during drive of the test site were always longer than those measured during fusion drives or ectopic drives. Since refractory periods measured during test site drive include latency, it could be argued that this was a factor in the observed refractory period prolongation. However, refractory periods measured during ectopic drives were progressively shorter as the distance between the drive site and the test site was increased. These findings cannot be explained by latency, since the refractory periods during ectopic drive were measured with respect to activation time of the test sites. The findings contradict reports by Han et al.[11, 12] that refractory periods were longer at sites distant to the origin of activation but are compatible with the effects of electrotonic interactions in terms of intracellular potential distributions described above.

Differences in action potential duration and refractory periods of various portions of the ventricles have been reported by several groups of investigators.[13-17] Differences in intrinsic recovery properties in various portions of the ventricles could have been a factor in the results we obtained. It is unlikely that it was the only factor, however. In pairs of observations in which two ectopic drives were symmetrically situated 2 and 6 mm from two refractory period test sites, the refractory periods were significantly longer when the test site was 2 mm from the drive site than when the test site was 6 mm from the drive site. This finding persisted when the location of the driving sites was switched from one end of the electrode array to the other.

On the basis of a two-dimensional model of cardiac fibers, Tanaka and Sasaki[18] reported that decay of electrotonic potentials was more abrupt when cell length was short. Matsuda and Hoshi[19] also studied electrotonic potentials and found a less steep decay of electrotonic effects along the longitudinal axis of Purkinje fibers than along the transverse axis. Woodbury and Grill[20] showed a similar directional difference of space constants in rat atrium. Clerc[21] reported that intracellular and extracellular resistances along the longitudinal fiber axis of papillary muscles were lower than those perpendicular to that axis. This would be expected to be associated with a longer space constant along the longitudinal fiber axis. Our findings are compatible with these reports. As distance between the driving and test sites was increased, the percent shortening of refractory periods was greater along the transverse than along the longitudinal axis of the heart. Fiber orientation on the epicardium of the apex of the left ventricle is parallel to the longitudinal axis of the heart during both systole and diastole.[22] The findings reported here are compatible with the difference in percent shortening of refractory periods along the two axes studied being related to fiber orientation, and with a greater length constant parallel to fibers.

In both intramural and epicardial observations, refractory periods measured when fusion of activation occurred near a test site were significantly shorter than those measured when the ventricle was driven from either of the fusion drive sites. These findings are also explicable on the basis of intracellular potential distributions. During fusion of activation, the site of fusion would repolarize later than other sites, provided variation in action potential durations did not exceed the conduction time between these sites. At the site of fusion, action potentials would be expected to shorten because the area of fusion of activation fronts would have a more negative intracellular distribution of potentials surrounding it than if activation propagated toward it from a single distant site.

When fusion of activation occurred near the driving sites, refractory periods were shorter than those obtained by driving the test site itself. This is in agreement with Abildskov's[7] findings. With decreasing distance between fusion and test sites, there was increasing reduction of refractory periods. These findings can also be explained on the basis of intracellular potential distributions. When fusion occurred near the driving site, sites distal to the area of fusion would have less negative intracellular potentials than they would have during drive of the test site alone. Therefore, when fusion was close enough to the driving site to affect it electrotonically, the sites distal to the area of fusion would lose the depolarizing effect exerted during test site drive. As the fusion front was nearer the driving site, less depolarizing effect would be expected and less prolongation of action potential duration at the driving site was observed. Thus, the shortening of refractory periods at the driving site in the presence of fusion of activation fronts was probably the result of loss of depolarizing electrotonic effects.

These experiments do not furnish direct evidence of electrotonic effects because electrotonic potentials themselves were not measured. However, all the findings are explicable on the basis of electrotonus, and the results were predictable from the intracellular distribution of potentials expected to be associated with each of the driving modes employed.

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