

# Characteristics and Possible Mechanism of Ventricular Arrhythmia Dependent on the Dispersion of Action Potential Durations

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**SUMMARY** The arrhythmogenic role of increased dispersion of repolarization (dispersion) was studied in 23 open-chest dogs using six simultaneously recorded monophasic action potentials (MAPs) from the ventricular surface and programmed ventricular premature stimulation (VPS). Increased dispersion was induced by generalized hypothermia (29°C) and regional warm blood (38–43°C) perfusion through a coronary artery branch. Hypothermia and regional warm blood perfusion increased maximum dispersion from  $13 \pm 10$  to  $111 \pm 16$  msec ( $p < 0.001$ ), predominantly because of the increased MAP duration difference ( $10 \pm 15$  vs  $97 \pm 16$  msec,  $p < 0.001$ ). The maximal difference between activation times was not significantly changed, but the QRS duration increased from  $47 \pm 6$  to  $52 \pm 7$  msec ( $p < 0.01$ ). Ventricular arrhythmia did not occur spontaneously but was induced by a single VPS in all 23 dogs during hypothermia and regional warm blood perfusion when dispersion reached a critical magnitude. The critical magnitude of dispersion required to induce ventricular arrhythmia was documented in 16 dogs by stepwise increments or decrements of dispersion. In four dogs, an increase in atrial pacing rate of 24 beats/min prevented induction of ventricular arrhythmia by decreasing dispersion from a critical magnitude of  $103 \pm 5$  msec to a nonarrhythmogenic value of  $86 \pm 9$  msec ( $p < 0.05$ ). In six dogs, we compared the stimulation site-dependent effects of VPS applied in the region with short and long MAPs. In all dogs, ventricular arrhythmia was inducible only by VPS from the region with a short MAP. Premature impulses from this region propagated more slowly than those from the region with a long MAP. Our results show that the large dispersion of repolarization facilitates the development of a conduction delay necessary to induce sustained arrhythmia by an early premature stimulus applied at the site with a short MAP.

STRONG experimental evidence links the vulnerability of ventricular myocardium to arrhythmia with increased temporal dispersion of refractoriness.<sup>1–5</sup> Conversely, it is believed that one of the beneficial effects of antiarrhythmic drugs relates to their ability to decrease dispersion.<sup>6</sup> Most of our knowledge concerning dispersion stems from studies in open-chest animals in which the sequence of recovery of excitability has been determined by sequential measurements of refractory periods at different sites. Another approach, suggested by Sarachek et al.,<sup>7</sup> consists of measuring the differences between the durations of simultaneously recorded monophasic action potentials (MAPs), which have the same shape and duration as transmembrane action potentials.<sup>8</sup> Simultaneous recording of MAPs permits direct measurement of the sequence of activation and repolarization of a propagated impulse. The technique also allows determination of the temporal relationship between the effective refractory period (ERP) and the duration of MAP, a relationship that is affected importantly by depolarization or antiarrhythmic drugs.

The purpose of this study was to assess the arrhythmogenic role of dispersion of repolarization using the technique of simultaneously recorded MAPs in dogs in which the increased dispersion of repolarization result-

ed predominantly from differences in MAP duration.

## Methods

We studied 23 mongrel dogs that weighed 19.1–32.7 kg and were anesthetized with i.v. sodium pentobarbital, 30 mg/kg. The chest was opened by a mid-sternal incision, and the dogs were ventilated with a Harvard respirator. The heart was suspended in a pericardial cradle. The sinus node was crushed and a bipolar Grass E2B platinum electrode was attached to the right atrial appendage for pacing at 100–158 beats/min (mean  $119 \pm 13$  beats/min). In 13 dogs, the pacing rate was maintained constant throughout the entire experiment at an average of  $116 \pm 10$  beats/min (range 100–140 beats/min), and in 10 dogs the pacing rate during hypothermia (see below) was slower than control, averaging  $113 \pm 7$  beats/min (range 100–120 beats/min).

Six suction electrodes were applied to record MAPs using the technique described previously.<sup>9, 10</sup> Electrode 1 was placed on the anterior surface of the right ventricle (RV); electrode 2 on the anterior surface of the left ventricle (LV) between the second diagonal branch and the distal branch of the left anterior descending coronary artery (LAD); electrode 3 on the anterior surface of the LV between the first and second diagonal branches of the LAD; electrode 4 on the anterior surface of the LV either medial or lateral to the first diagonal branch of the LAD; electrodes 5 and 6 were placed on the anterolateral surface near the obtuse margin of the LV (fig. 1). Electrodes 2–6 were arranged 1–2 cm apart along a line parallel to the cardiac margin. Electrodes 1 and 2 were 2–4 cm apart.

In addition, 12 local electrograms were recorded

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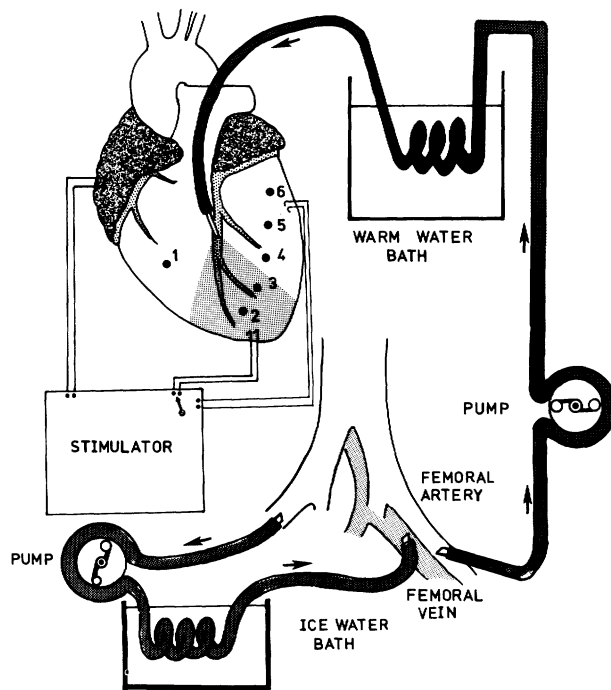


FIGURE 1. *The experimental setup. The six black dots mark the position of suction electrodes on cardiac surface. The shaded area represents the approximate region perfused by the left anterior descending coronary artery (LAD) distal to the site of the cannula insertion. Regional warm blood perfusion is achieved by pumping the arterial blood circulating through a warm water bath into the LAD through a cannula. Cooling is achieved by pumping arterial blood circulating through an ice water bath through a cannula inserted into femoral vein. Stimulating electrodes are placed on the right atrial appendage and at two sites on the left ventricle.*

using 12 bipolar plunge electrodes in 21 dogs at the following locations: two near (within 5 mm) the site of MAP 1 (one subepicardial and one subendocardial); one subepicardial at the midpoint between MAP 1 and MAP 2; three near MAP 2 (one subepicardial, one intramural and one subendocardial); one subepicardial near MAP 3; two near MAP 4 (one subepicardial and one subendocardial); one subepicardial near MAP 5; and two near MAP 6 (one subepicardial and one subendocardial). In two dogs, the arrangement of the plunge electrodes was modified to increase the number of subendocardial recording sites by transferring the two electrodes near MAP 3 and MAP 5, one to a subendocardial location near the apex of LV and the other to a subendocardial location near the site of coronary cannulation. We also recorded an ECG orthogonal Y lead of the system designed for the dog by McFee and Parungao.<sup>11</sup> The signals were recorded with a Gould universal preamplifier and amplifier (model 13-4615-56); the frequency response was set at 0.5–1 Hz for MAPs, 30–300 Hz for local electrograms, and 0.05–300 Hz for the ECG. Six MAPs and one ECG lead were recorded simultaneously with a Gould Brush 2800 recorder. The same ECG lead and local electrograms were recorded simultaneously with a multichan-

nel Honeywell 1858 fiberoptic recorder. Both recorders were synchronized, and both sets of signals were registered at a paper speed of 200 mm/sec. Our criteria for acceptance of the MAPs were (1) amplitude greater than 15 mV,<sup>12</sup> (2) smooth repolarization course, (3) during regular pacing the durations and shapes of MAPs were identical in 10 consecutive complexes and (4) atrial and ventricular pacing produced MAPs of the same duration and with the same slope of phase 3. The experiments were acceptable when all MAPs remained acceptable during the entire programmed stimulation, which lasted 15–30 minutes. If a MAP became unacceptable during the interval between procedures, a new record was made in the immediate vicinity of the previous site of suction application. The new MAP was acceptable if its duration was within 5 msec of the previously recorded MAP. The protocol was successfully completed in 23 of 56 dogs.

The end of the MAP was defined as the point of intersection of the baseline with the tangent to the steepest part of terminal repolarization.<sup>9</sup> The activation time (AT) was measured as the interval from the beginning of the QRS complex to the onset of the steep upstroke of the MAP.<sup>9,10</sup> When the beginning of the MAP was distorted during ventricular pacing or premature stimulation, the AT in the local electrogram was used to identify the onset of activation at the site of MAP recording. This point was defined as the peak or the nadir of the first high-frequency deflection in the electrogram. The error for the measurement of the AT and for the MAP duration was within 5 msec. This was determined by repeated measurements made by the same observer and by independent measurements by several different observers.

Dispersion of ventricular repolarization was measured directly as the difference between the ends of simultaneously recorded MAPs. Each value of dispersion could result from MAP duration differences alone, AT differences alone, or added contributions of MAP duration and AT differences.

For ventricular pacing or programmed ventricular premature stimulation (VPS) during atrial pacing, two bipolar pacing electrodes were attached to the left ventricle, one within 5 mm of MAP 2 (paraseptal site) and the other within 5 mm of MAP 6 (lateral site) (fig. 1). To pace the atrium and the ventricle, we used rectangular 2-msec pulses at twice diastolic threshold strength. For VPS, we used stimuli of twice diastolic threshold to scan diastole, starting in late diastole, at intervals decreasing by 10–20 msec until the effective refractory period (ERP) was reached. After reaching the ERP, the stimulus strength was increased to four times diastolic threshold, and the VPS was repeated scanning early diastole at intervals that decreased by 10 msec. After reaching the ERP for this stimulus strength, the procedure was repeated using a stronger stimulus. The following strength of stimulation were used in succession in each run: two times, four times, six times, eight times, 10 times diastolic threshold, 5 mA, 10 mA, 15 mA, 20 mA, 25 mA, 30 mA, 35 mA and 40 mA. The threshold of diastolic excitability of

the ventricle was  $0.14 \pm 0.06$  mA during control,  $0.19 \pm 0.09$  mA during hypothermia and  $0.24 \pm 0.06$  mA during selective coronary artery perfusion with heated blood. In eight dogs, strength-interval curves were plotted to determine the relation between MAPD and ERP. In these experiments the stimulation site was within 5 mm of the MAP recording site.

To change action potential duration, we altered the myocardial temperature by general hypothermia or by selective coronary artery perfusion with heated blood. For generalized hypothermia, a shunt between the right femoral artery and the left femoral vein was established (fig. 1). The shunted blood was cooled with ice water to decrease the temperature in the left atrium from  $34\text{--}35^\circ\text{C}$  to  $29\text{--}30^\circ\text{C}$ . For regional warm blood perfusion (RWBP), a shunt was established between the left femoral artery and the LAD between the origins of the first and second diagonal branches (fig. 1). In none of the acceptable experiments did the establishment of the femoral artery to coronary artery shunt produce changes in the ECG, AT, MAPs, arrhythmia, discoloration of the myocardium, or visible changes in myocardial motion. The shunt flow was regulated by a pulsatile pump (Cole-Palmer Instrument, model 7564-10) and ranged from 75 to 100 ml/min. The shunted blood passed through a coil immersed in a  $45^\circ\text{C}$  bath. The blood temperature was regulated by varying the length of the coil immersed in the bath. This temperature range was  $38\text{--}43^\circ\text{C}$  at the outlet of the shunt immediately before entering the LAD.

In three dogs, the myocardial mass perfused by the warm blood was estimated after injecting dye through the coronary cannula. The weight of myocardium stained by the dye was 15.4–27% of the combined weight of both ventricles.

### Experimental Design

Tests consisted of programmed VPS at each of the two sites, paraseptal and lateral, under the following experimental conditions: control, hypothermia, hypothermia combined with RWBP, and RWBP alone. The tests under control conditions and hypothermia were completed in all 23 dogs. Subsequent tests were performed as follows:

Hypothermia at a constant temperature and RWBP at two to six temperatures associated with two to six magnitudes of dispersion (59 tests in 16 dogs). VPS was applied at the paraseptal site only.

Hypothermia at a constant temperature and RWBP at a constant temperature, using two different atrial pacing rates (eight tests in four dogs). VPS was applied at the paraseptal site only.

Hypothermia at a constant temperature and RWBP at a constant temperature (12 tests in six dogs). VPS was applied at both paraseptal and lateral sites.

RWBP alone. Tests were made after completion of the tests during hypothermia combined with RWBP, and subsequent discontinuation of hypothermia while continuing RWBP at the same temperature (four tests in four dogs). VPS was applied at the paraseptal site only.

### Statistical Methods

The statistical probability of differences between means was calculated using unpaired and paired *t* tests. When more than two groups were compared, analysis of variance was used. When multiple comparisons were made, the *t* test was modified by the Bonferroni method. When the compared data included samples of fewer than 10, we used Wilcoxon's test for unpaired, and in some instances, for paired data. When the *p* value after Wilcoxon's test was higher than after *t* test, the Wilcoxon's *t* test is reported. When appropriate, linear regression analysis was also used.

### Definitions

*Dispersion.* Dispersion of repolarization measured (in msec) as the temporal difference between the ends of simultaneously recorded MAPs.

*Basic dispersion.* The dispersion measured during atrial pacing.

*Premature dispersion.* The dispersion measured during VPS.

*Maximum dispersion.* The greatest dispersion between any two of six simultaneously recorded MAPs.

*Adjacent dispersion.* The dispersion between two adjacent sites on the left ventricle separated by 1–2 cm.

*Critical maximum dispersion.* The least maximum dispersion at the time of induction of repetitive ventricular responses after a single premature stimulus.

*Effective refractory period (ERP).* ERP at the testing site was defined as the longest interval between the onset of depolarization of a basic atrial pacing complex and the testing premature stimulus that failed to elicit a propagated response.

## Results

### Control and Hypothermia

The average control values in 23 dogs during atrial pacing at an average cycle length of  $503 \pm 52$  msec (range 380–600 msec) were as follows: QRS duration  $47 \pm 6$  msec (range 40–60 msec); maximal differences in AT  $26 \pm 10$  msec (range 7–42 msec); MAP duration  $246 \pm 23$  msec (range 185–290 msec); and maximum dispersion  $13 \pm 10$  msec (range 0–35 msec).

Hypothermia increased the QRS duration to  $56 \pm 7$  msec (range 40–70 msec), the maximal differences in AT to  $32 \pm 11$  msec (range 12–48 msec), and the MAP duration to  $302 \pm 26$  msec (range 230–235 msec). All of the above values were significantly different from control. Hypothermia did not appreciably change the morphology of the QRS complexes. The maximum dispersion averaged  $17 \pm 14$  msec (range 0–40 msec), and was not significantly different from control. In 10 dogs, the rate of pacing during hypothermia was kept slower than in control. However, we found no significant difference between the results in these 10 dogs and in the remaining 13 dogs. Table 1 shows the MAP durations from the region not perfused by the warm blood and the region perfused by the cannulated LAD branch, as well as the maximum dispersion in the 13 dogs in which the pacing rate was kept constant. Hypothermia prolonged MAP duration

TABLE 1. *The Monophasic Action Potential Duration and the Maximal Dispersion of Ventricular Repolarization During Control, Hypothermia, and Hypothermia and Regional Warm Blood Perfusion in 13 Dogs*

	Control	Hypo- thermia	Hypo- thermia + RWBP
MAP-P (msec)	252 ± 22 (210–285)	301 ± 26 (255–335)	171 ± 19 (130–195)
MAP-NP (msec)	246 ± 22 (210–285)	292 ± 30 (250–340)	270 ± 24 (230–325)
Dispersion (msec)	14 ± 12 (0–35)	14 ± 12 (0–40)	114 ± 17 (95–145)

Values are mean ± SD.

\* $p < 0.001$ .

† $p < 0.005$ .

Abbreviations: MAP-P = monophasic action potential from the perfused area; MAP-NP = monophasic action potential from the region not perfused by the warm blood; RWBP = regional warm blood perfusion.

equally in both regions and did not change the maximum dispersion. Ventricular arrhythmia did not occur either spontaneously or during VPS from either the paraseptal or the lateral site.

#### Hypothermia Combined with Regional Warm Blood Perfusion

When RWBP was added to hypothermia, the resulting changes depended on the temperature differences. When the temperature difference was maximal in 23 dogs, the QRS duration was  $52 \pm 7$  msec (range 40–67 msec), and the maximal difference in AT was  $27 \pm 10$  msec (range 6–41 msec). Both values were significantly smaller than the corresponding values during hypothermia alone ( $p < 0.05$  for QRS duration and  $p < 0.01$  for the maximal difference in AT). The QRS duration was also significantly longer than control ( $p < 0.01$ ), but the maximal difference in AT was not significantly different from control. The QRS morphology was not appreciably changed in the nonpremature complexes, but was sometimes altered in the early premature complexes. The maximum dispersion averaged  $111 \pm 16$  msec (range 90–145 msec) and was significantly greater than during control or hypothermia ( $p < 0.001$ ). Changes in MAP duration were dependent on the location of recording sites: RWBP shortened MAP in the perfused region and either did not change or slightly shortened MAP in the region not perfused by the warm blood. The MAP in the perfused

region shortened more than in the region not perfused by the warm blood (table 1). The slight shortening in the region not perfused by the warm blood was probably due to collateral communication between the first and the second diagonal branches of the LAD and between the left circumflex and the LAD. Ventricular arrhythmia did not occur spontaneously during hypothermia combined with RWBP.

#### Induction of Ventricular Arrhythmia: Critical Role of Dispersion

In each dog, when maximum dispersion reached a certain critical value, an early premature ventricular stimulus applied at the paraseptal site induced repetitive ventricular responses that always progressed to ventricular fibrillation. The stimulus strength of the premature response that induced arrhythmia ranged from 0.4 to 40 mA (average  $9.5 \pm 11$  mA). To test the relation between the magnitude of dispersion and the ability to induce ventricular arrhythmia, we compared the effects of two or more different magnitudes of dispersion in the same dog in the following series of experiments.

**Graded RWBP.** In 16 dogs, hypothermia was maintained at a constant temperature while blood temperature during RWBP was increased stepwise to produce graded increases in dispersion. The number of steps of induced dispersion in different dogs was as follows: six in one, five in one, four in seven, three in six, and two in one (fig. 2). During control, maximum dispersion was 30 msec (panel A); during stepwise temperature increase, maximum dispersion was 60 msec, 105 msec, and 110 msec (panels B–D). In panels A, B and C, ventricular arrhythmia could not be induced by the earliest premature stimulus from the paraseptal site. However, in panel D, an early premature stimulus from the paraseptal site induced ventricular fibrillation. Similar results were observed in 15 other dogs. In these 16 dogs, the critical maximum dispersion averaged  $112 \pm 15$  msec (range 95–145 msec).

**Withdrawal of hypothermia.** In four dogs, the effects of VPS were tested during RWBP both with and without hypothermia. During hypothermia combined with RWBP, the critical maximum dispersion values associated with induction of ventricular fibrillation were 105, 115, 120 and 125 msec. After defibrillation, RWBP was continued but hypothermia was withdrawn. This decreased the respective values of maximum dispersion to 60, 85, 65 and 60 msec, and it was no longer possible to induce ventricular arrhythmia in any of the four dogs.

**Increase in atrial pacing rate.** In the presence of constant hypothermia and RWBP, the atrial pacing rate was increased in four dogs. During pacing at a cycle length of  $510 \pm 70$  msec (range 450–580 msec), maximum dispersion was  $103 \pm 5$  msec (range 100–110 msec). When the pacing cycle length was decreased by 50–130 msec to an average of  $423 \pm 39$  msec (range 380–450 msec), dispersion decreased to  $86 \pm 9$  msec (range 75–95 msec) ( $p < 0.05$ ). This decrease occurred because the shorter MAP within the

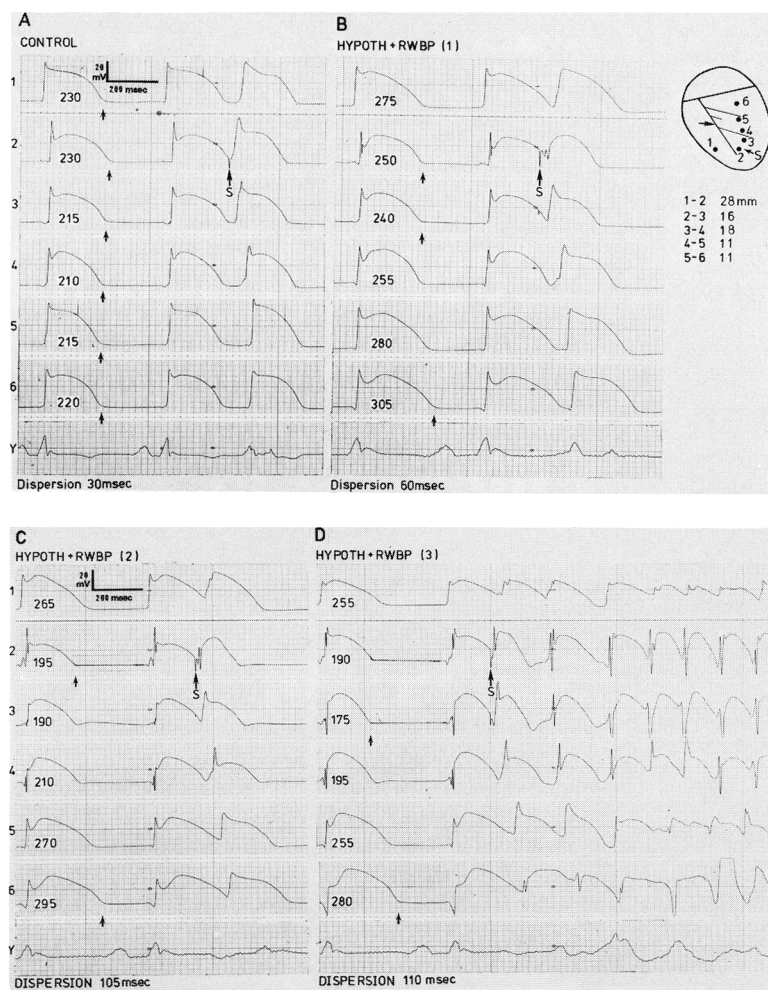


FIGURE 2. An experiment in which dispersion was progressively increased until ventricular arrhythmia was induced. (A) Control. (B–D) Hypothermia combined with regional warm blood perfusion (RWBP). The temperature of the hypothermia was kept constant while the temperature of the perfusion blood during RWBP was progressively increased from B to D. The schematic diagram to the right of panel B shows the location of six suction electrodes and the interelectrode distances. The arrow on the left side of the diagram shows the site of coronary cannulation and that on the right side, labeled S, the site of ventricular premature stimulation (VPS). In each panel, short vertical arrows show the end of monophasic action potentials (MAPs). The maximum dispersion as defined by the maximal difference between the ends of any two of six MAPs is shown at the bottom of each panel. The longer arrows labeled S show the stimulus of VPS. Numbers within each MAP represent their duration in msec. In each panel, the first two complexes are the basic complexes during atrial pacing, and the third complex is the premature complex in response to VPS. Note the onset of spontaneous tachycardia after the VPS in panel D. Stimuli in panels A–C represent the strongest (40 mA) and the most premature stimuli that elicited a premature ventricular complex.

170–205-msec range shortened less than the longer MAPs within the 245–295-msec range. The average shortening of the short MAPs was 14 msec ( $188 \pm 20$  msec vs  $174 \pm 17$  msec), and of the long MAPs 31 msec ( $266 \pm 22$  msec vs  $235 \pm 15$  msec). The maximal difference in AT did not change ( $32 \pm 7$  msec at slow pacing rate and  $32 \pm 8$  msec at fast pacing rate). In each dog, ventricular fibrillation was induced during pacing at a slower rate but not during pacing at a faster rate. Figure 3 shows a representative experiment.

#### Relation Between the Site of VPS and the Induction of Arrhythmia

The effects of the site of VPS were compared in six dogs. In each dog, ventricular fibrillation was induced during VPS at the paraseptal site (fig. 4B) in the presence of a critical maximum dispersion of 100–145 msec (average  $118 \pm 16$  msec), but no arrhythmia could be induced by VPS at the lateral site in the presence of the same dispersion (fig. 4A).

We analyzed the magnitude of dispersion and its components, the AT difference and the MAP duration difference in the premature ventricular complexes from each of the two stimulation sites in these six dogs. The maximum dispersion of repolarization of ventricu-

lar complexes induced by premature stimuli at the paraseptal and lateral sites were analyzed by separating it into two contributing components, the AT difference and the MAP duration difference (table 2). The value of AT difference contributing to the maximum dispersion is not necessarily the same as the value of the maximal difference in AT because these two values may be derived from different sets of recording sites. Not shown in the table is that MAP duration during atrial pacing was 210–290 msec during control, 265–345 msec during hypothermia, and 170–350 msec during hypothermia combined with RWBP. Table 2 shows that the basic dispersion in control and during hypothermia did not differ significantly from each other. Under both conditions, the dispersion averaged about 30 msec, and resulted predominantly from MAP duration difference. The basic dispersion during hypothermia combined with RWBP averaged 102 msec. The contribution of MAP duration difference to this dispersion averaged 77.5% and the contribution of AT difference 22.5%. VPS at both sites significantly increased the dispersion under all three experimental conditions, as a result of an increased AT difference (average increase 51–108 msec) without a significant additional increase in the MAP duration difference. During control and during hypothermia, the AT differ-



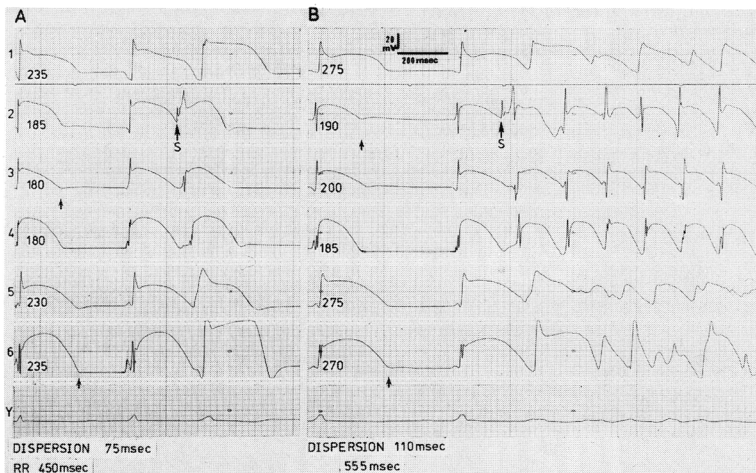


FIGURE 3. Effects of atrial pacing rate on the maximum dispersion and the induction of ventricular arrhythmia. The cycle length during atrial pacing is 450 msec in panel A and 555 msec in panel B. Ventricular arrhythmia was induced only at a slower atrial pacing rate when the maximum dispersion was greater. The stimulus in panel A represents the strongest (40 mA) and the most premature stimulus that elicited a premature ventricular complex. Symbols are as in figure 2. RR = cycle length of basic atrial pacing.

ence at the lateral site was greater than at the paraseptal site. This could be attributed to the greater distance between the stimulation site and the most distant recording site (fig. 1), because the maximum dispersion was present between locations 6 and 1 during VPS at the lateral site and between locations 2 and 6 or 2 and 1 during VPS at the paraseptal site (fig. 2A). However, during hypothermia combined with RWBP, the inter-electrode distance was unchanged, but the AT difference was greater at the paraseptal site than at the lateral site.

The critical, maximum dispersion preceding the onset of spontaneous ventricular arrhythmia averaged 176 msec (table 2). This magnitude of dispersion was induced by the premature stimuli from the paraseptal site during hypothermia combined with RWBP. Premature stimuli failed to induce critical dispersion in the control state and during hypothermia, apparently because the underlying basic dispersion was not large, while the failure to induce critical dispersion by premature stimuli from the lateral site during hypothermia combined with RWBP was apparently due to an insufficient increase in the AT difference. Thus, the occurrence of critical dispersion required both a large basic dispersion and an appropriate increase in the AT difference that occurred during premature stimulation from the site with short MAP durations. The site-dependent

differences in maximal premature dispersion (table 2) were corroborated by the changes of dispersion at adjacent sites.

#### *Effect of Stimulation Site on the Activation Pattern of Ventricular Complex in the Presence of an Increased Basic Dispersion*

We studied the effect of stimulation site on the activation pattern of the ventricular complex at 12 different recording sites in four dogs in which VPS was performed during hypothermia combined with RWBP and RWBP alone. VPS was applied at each of the two stimulation sites during hypothermia combined with RWBP, and at the paraseptal site only during RWBP alone. In each dog, hypothermia combined with RWBP produced a critical dispersion of 105–125 msec (fig. 5). We chose the site of the earliest activation as the reference point for the AT at the remaining recording sites. The recording sites were located in one of the following regions: perfused with warm blood, not perfused with warm blood, and the border area located within 1 cm on each side of the assumed divide between the arterial supply of the cannulated LAD and the first diagonal branch of the LAD. In the experiment shown in figure 5, the AT is plotted on the ordinate and the coupling interval of the VPS on the abscissa during stimulation from the paraseptal site (fig. 5A) and from

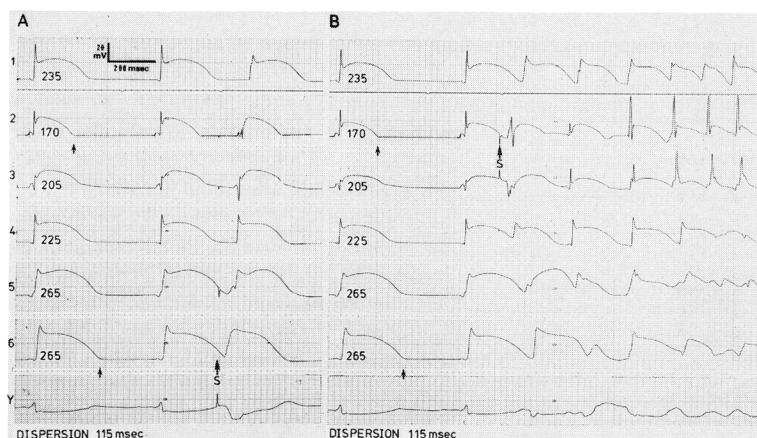


FIGURE 4. Effect of site of ventricular premature stimulation (VPS) on the induction of ventricular arrhythmia in the presence of critical dispersion. (A) VPS at the lateral site. (B) VPS at the paraseptal site. The stimulus in A represents the strongest (40 mA) and the most premature stimulus that elicited a premature ventricular complex. Ventricular arrhythmia was induced in B but not in A. Symbols are as in figure 2.

TABLE 2. Basic and Premature Dispersion of Repolarization Contributions of Mean Action Potential Duration Difference and Activation Time Difference

Type of pacing	Control				Hypothermia			
	No. of measurements	Disp	MAPD diff	AT diff	No. of measurements	Disp	MAPD diff	AT diff
Atrial	9	32 ± 10	27 ± 10	4 ± 9	8	29 ± 5	27 ± 11	1 ± 12
Atrial + VPS L	8	106 ± 11	25 ± 16	81 ± 11	6	132 ± 24 <sup>a</sup>	24 ± 21	108 ± 9 <sup>b</sup>
Atrial + VPS PS	9	89 ± 16	23 ± 13	66 ± 11	7	119 ± 40 <sup>a</sup>	33 ± 35	86 ± 19 <sup>b</sup>

Values are mean ± SD (in msec).

\* $p < 0.01$  Atrial + VPS L vs Atrial + VPS PS.

† $p < 0.001$  Atrial + VPS L vs Atrial, or Atrial + VPS PS vs Atrial.

‡ $p < 0.05$  Atrial + VPS L vs Atrial + VPS PS.

<sup>a</sup> $p < 0.05$  H vs control.

<sup>b</sup> $p < 0.01$  H vs control.

<sup>c</sup> $p < 0.001$  H + RWBP vs control.

<sup>d</sup> $p < 0.005$  H + RWBP vs control.

<sup>e</sup> $p < 0.05$  H + RWBP vs control.

<sup>f</sup> $p < 0.01$  H + RWBP vs control.

<sup>g</sup> $p < 0.01$  H + RWBP vs H.

<sup>h</sup> $p < 0.005$  H + RWBP vs H.

<sup>i</sup> $p < 0.001$  H + RWBP vs H.

Abbreviations: MAPD diff = monophasic action potential duration difference; Disp = dispersion of repolarization; AT diff = activation time difference; RWBP = regional warm blood perfusion; VPS L = ventricular premature stimulation at the lateral site; VPS PS = ventricular premature stimulation at the paraseptal site.

the lateral site (fig. 5B). The shortest coupling interval was 185 msec at the paraseptal site and 265 msec at the lateral site. Figure 5A shows that at the sites within the perfused area, the shortening of the coupling interval was associated with no change or an increase in AT of less than 10 msec. At the sites within the region not perfused with warm blood, the coupling interval was associated with a progressive increase in AT. At the sites within the border area, shortening of the coupling interval produced variable AT changes: At four sites the changes were similar to those at the sites within the region perfused with warm blood, and at the other two sites the changes were similar to those at the sites within the region not perfused with warm blood. Figure 5B shows that VPS at the lateral site caused either no change or less than a 10-msec increase in AT at all recording sites.

When hypothermia was discontinued in the experi-

ment shown in figure 5, the dispersion decreased to 60 msec. Stimulation site-dependent differences in AT at various recording sites were still present but became less pronounced (fig. 6).

#### Contribution of the AT Differences to the Dispersion Between Two Adjacent Interelectrode Sites on the Left Ventricular Surface

In eight of 24 pairs of adjacent sites in six dogs, the graded increases in temperature induced four or more magnitudes of adjacent dispersion. At these sites, we correlated the maximum AT difference during premature stimulation at the paraseptal site with the underlying adjacent basic dispersion between the same sites. In each pair, one recording electrode was located in the border region between the warm blood perfused region and the region not perfused with the warm blood, and the other electrode in the perfused region in four and in

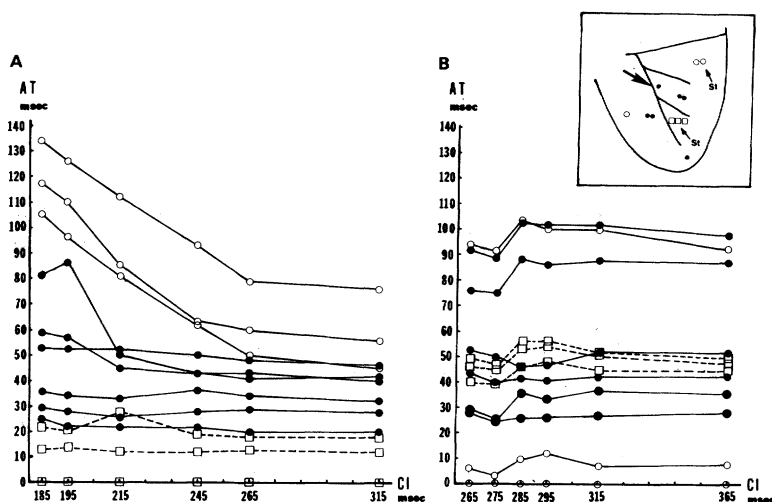


FIGURE 5. Results of an experiment showing the activation times (AT) at 12 recording sites during ventricular premature stimulation (VPS) at the paraseptal site (A) and at the lateral site (B) at different coupling intervals (CI) in the presence of critical dispersion. The diagram in the inset shows the locations of recording sites. Squares indicate the perfused area, solid circles the border area, open circles the nonperfused area, small arrows the site of VPS (St), and the large arrow the site of coronary cannulation.

TABLE 2. (Continued)

Hypothermia and regional warm blood perfusion			
No. of measurements	Disp.	MAPD Diff	AT Diff
10	102 ± 29 <sup>c,i</sup>	79 ± 29 <sup>c,i</sup>	23 ± 14 <sup>d,h</sup>
7	127 ± 39 <sup>c</sup>	76 ± 25 <sup>c,g</sup>	51 ± 50 <sup>f,g</sup>
8	176 ± 28 <sup>c,g</sup>	76 ± 11 <sup>c,g</sup>	100 ± 20 <sup>c</sup>

the nonperfused region in the remaining four pairs (fig. 7). The maximal AT difference between the two adjacent sites in premature complexes is plotted on the ordinate and the dispersion between these two sites during atrial pacing on the abscissa in figure 7. The dot on the far left represents the control value, which has a negative sign because the MAP at the site closer to the stimulation site ended later than the MAP at the more distal site. With progressive increases in the temperature of the perfusing blood, the basic adjacent dispersion increased progressively by 10, 35, 40 and 50 msec, while the corresponding AT differences increased by 1, 15, 25 and 47 msec. The correlation coefficient for the relation between these two variables in this example was 0.82 ( $p < 0.001$ ). For the other

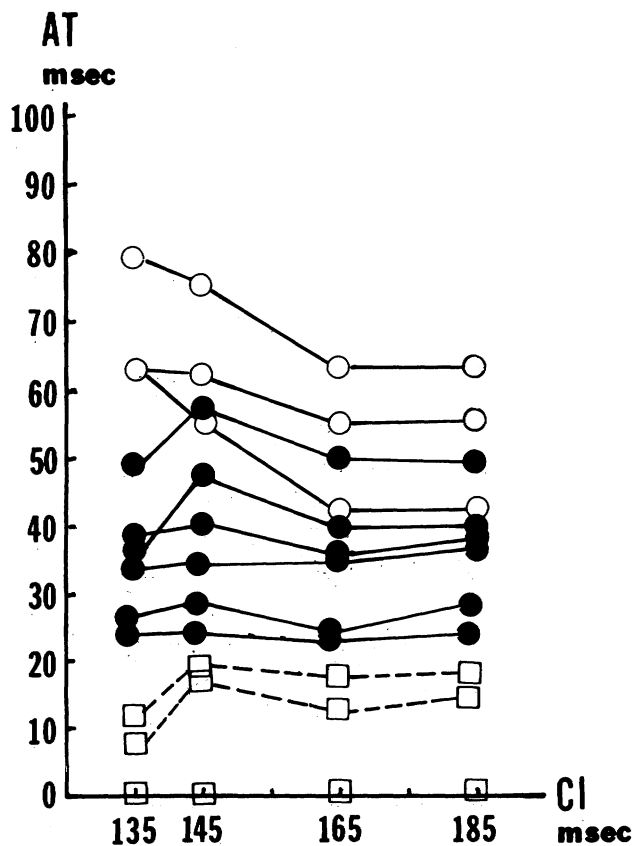


FIGURE 6. Activation times (AT) at 12 recording sites during ventricular premature stimulation at the paraseptal site at different coupling intervals (CI) during regional warm blood perfusion without hypothermia in the same dog as in figure 5. The locations of recording sites were the same as in figure 5.

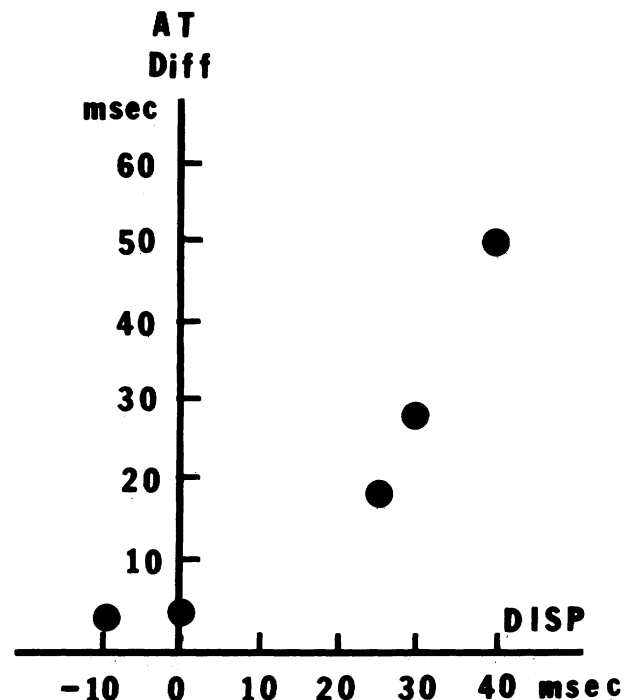


FIGURE 7. Relation between the dispersion between two adjacent recording sites during atrial pacing (abscissa) and the activation time difference (AT Diff) between the same recording site during ventricular premature stimulation (ordinate) in one dog.

seven pairs of sites the results were similar ( $r = 0.89-0.99$ ,  $p < 0.05-0.001$ ). There was no significant correlation between the AT differences and the basic dispersion during premature stimulation at the lateral site for any of these pairs of adjacent sites.

In the remaining 16 pairs of adjacent sites in these six dogs, both electrodes were located either within the region perfused or not perfused by warm blood. At these sites, the numbers of distinctly different magnitudes of adjacent dispersion were smaller and not sufficient for statistical analysis, probably because of the lesser myocardial temperature difference between the sites. However, there was not a single pair of adjacent sites at which the AT difference decreased after the increase of basic dispersion by the hypothermia combined with RWBP.

#### Activation During Spontaneous Ventricular Activity

We compared the site of the earliest activation of the first spontaneous ventricular complex of tachycardia with that of the premature ventricular complex (PVC) that induced this spontaneous activity. For this, adequate records were available in 18 episodes of ventricular fibrillation induced in 13 dogs. In three of these episodes, the sites of the earliest activation of the first spontaneous ventricular complex and of the preceding stimulus-induced PVC were the same, and in the remaining 15 episodes the sites differed. When the sites differed, the earliest activation of the first spontaneous complex was recorded in the perfused region in six, in



the border region in six, and in the region not perfused with warm blood in the remaining three episodes.

Figure 8 shows a record from one of the two dogs in which the plunge electrode arrangement was modified (see Methods). During the activation of the first spontaneous complex ( $R_1$ ), the earliest activation site was in the border region; this and seven other sites were activated earlier than the site of the earliest activation (site 4) of the stimulated complex ( $S_1$ ). Also, the activation appears to have spread from more than one direction, for site 3e, located on the right ventricle, and site 9, on the left ventricle, although separated by 4 cm, were activated at the same time. A similar pattern of activation was recorded in the other dog with the same arrangement of recording electrodes.

### Relation Between MAP Duration and ERP

We tested whether the dispersion of repolarization measured by MAP reflected the dispersion of refractoriness under the experimental conditions described in this paper. Figure 9 shows an experiment in which the strength-interval relation was tested near the site of MAP recording. The sites of stimulation and of the MAP recording were maintained constant but the con-

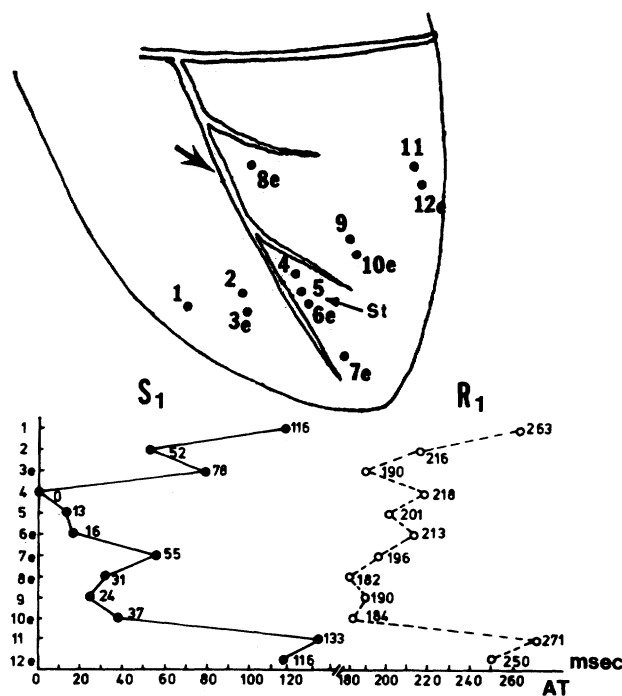


FIGURE 8. Activation sequence of the ventricular complex in response to a ventricular premature stimulation ( $S_1$ ) and that of the first spontaneous ventricular complex ( $R_1$ ) in the presence of critical dispersion in one dog. Schematic diagram shows the location of the plunge electrodes; e indicates subendocardial location. Three pairs of electrodes (2 and 3e, 9 and 10e, and 11 and 12e) are at the same location; one electrode of the pair is subepicardial, and the other subendocardial. Electrodes 4, 5 and 6e are at the same location; 4 is subepicardial, 5 intramural and 6e subendocardial. The thin arrow shows the site of VPS and the thick arrow the site of coronary cannulation. The activation times (AT) at each location were measured in reference to the site of earliest activation (electrode 4) of  $S_1$ .

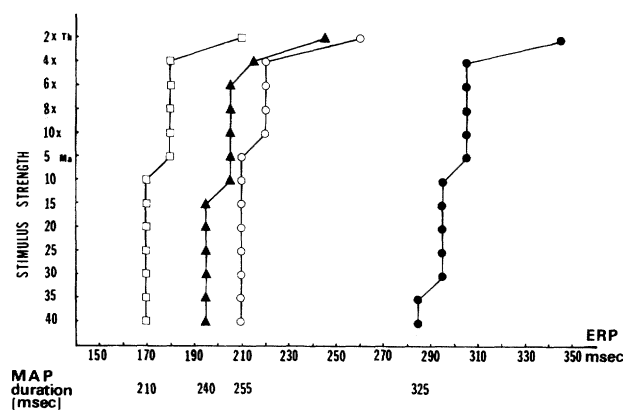


FIGURE 9. Strength-interval curves and duration of monophasic action potential (MAP) recorded at a site within 5 mm from the stimulation site during control, hypothermia and regional warm blood perfusion. The effective refractory period (ERP) at each strength of stimulus is plotted against the strength of stimulus. The division on the ordinate is not a proportional scale and the strength of the stimulus is expressed in milliamperes (mA) in the lower portion of the ordinate and in the multiples of the threshold of diastolic excitability ( $Th$ ) in the upper portion when the stimulus strength ranged from twice to 10 times  $Th$ . The MAP durations corresponding to each strength-interval curve are shown at the bottom of the figure. The 255-msec MAP was recorded during control, the 325-msec MAP during hypothermia and MAPs of 240 and 210 msec during regional warm blood perfusion.

trol MAP duration of 255 msec was either shortened to 240 and 210 msec by warm blood perfusion or lengthened to 325 msec by hypothermia. In figure 9, the strength-interval curves were nearly parallel to each other. The differences between MAP duration and the duration of ERP were 40–45 msec and did not differ from each other by more than 5 msec. Similar results were obtained in four other experiments and also within a wide range of premature complexes in three experiments. In these three experiments, the nearly constant individual differences between MAP duration and ERP were 30, 35 and 50 msec.

### Discussion

The role of increased dispersion of refractoriness in cardiac arrhythmias has been investigated after administration of pharmacologic agents such as quinidine, digitalis, chloroform or catecholamines, and interventions such as sympathetic stimulation, intracoronary infusion of potassium and cooling and warming of the cardiac surface.<sup>1-3, 5, 13</sup> It may be difficult, or perhaps impossible, to design experimental conditions that would alter the dispersion of refractoriness alone without a concomitant change in other electrophysiologic properties, i.e., conduction or excitability.<sup>4</sup> Nevertheless, it appeared to us that it may be feasible to create a model in which the dominant component of nonhomogeneity would result from the differences between action potential durations and would reflect the dispersion of refractoriness. To achieve this, we modified the "thermal lesion" models used to test the role of dispersion of refractoriness in the genesis of ventricular

arrhythmia<sup>3, 13</sup> or to measure the effect of dispersion of refractoriness on ventricular fibrillation threshold.<sup>4</sup>

Compared with previous studies involving the cooling and the warming of myocardium,<sup>3, 13</sup> we operated within a more limited temperature range (29–43°C). Within this temperature range, the principal cause of increased dispersion of repolarization was the increased MAP duration difference (tables 1 and 2). The concomitant changes in conduction as evidenced by changes in QRS duration and AT differences were less pronounced. Also, the temperature alterations within this range caused only slight changes in myocardial excitability without an appreciable change in temporal relation between the strength-interval curve and the duration of MAP (fig. 9). These results were consistent with the effects of comparable temperature changes on the electrophysiologic properties in cardiac Purkinje<sup>14</sup> and ventricular fibers.<sup>15</sup> In the Purkinje fibers, the  $Q_{10}$  for upstroke velocity was 1.7, for the duration of plateau 4.5, and for the duration of terminal repolarization 2.6.<sup>14</sup> In the *in situ* canine ventricle,<sup>15</sup> temperature changes within the range comparable to that in our study produced large changes in action potential duration, while the changes in QRS duration appeared negligible (figure 4 in reference 15), and the diastolic excitability was unchanged.<sup>15</sup> In either fiber type, the resting membrane potential was unchanged within the temperature range used in our study.<sup>14, 15</sup> However, we cannot rule out the possibility that the temperature had a more pronounced effect on conduction in the early premature complexes than in the nonpremature complexes. Gettes and Reuter<sup>16</sup> found that in isolated guinea pig papillary muscles the  $Q_{10}$  for steady-state  $dV/dt$  max was 1.8–2.5, and for the time constant of the recovery of  $dV/dt$  max from inactivation 2.8–4.2, within the potential range of –84 to –65 mV.

#### Evidence That the Arrhythmia Induction was Dependent on the Dispersion of Repolarization

By grading dispersion in our preparation, we have shown that ventricular arrhythmia could be induced in each dog by a single stimulus only at a certain critical degree of dispersion of repolarization. When the magnitude of this dispersion was reduced by discontinuing hypothermia or increasing the rate of atrial pacing, ventricular arrhythmia was no longer inducible. Pertinent to our results are the studies of Allesie *et al.*,<sup>17</sup> who examined the role of accurately graded dispersion on arrhythmia in isolated superfused rabbit atria where a circus movement tachycardia occurred as a result of unidirectional block during the propagation of a premature impulse. Using graded concentrations of carbamylcholine, which decreased the dispersion, these investigators accurately established the magnitude of dispersion in the refractory period between neighboring areas that was critical for the occurrence of arrhythmia. However, the occurrence of circus movement tachycardia in their preparation required not only a certain critical degree of dispersion of refractory periods, but also an extended area in which the refractory period was prolonged. Judging from the extent of the surface area in which the MAP duration was pro-

longed, it appears to us that this requirement was probably fulfilled also in our experimental model.

We believe that by cooling and warming the blood rather than the cardiac surface, we have avoided large transmural temperature gradients and therefore have sampled the representative regions with the extremes of long and short MAPs. However, the small number of recording sites on the ventricular surface makes it impossible to assess the relation between the measured values and dispersion within the entire heart. Similarly, we have no information about the duration of repolarization in Purkinje fibers and their possible role in dispersion.

#### Possible Mechanism of Induced Arrhythmia

In the presence of critical dispersion ranging from 95 to 145 msec, the differences between the duration of the longest and shortest MAPs averaged 99 msec (table 1). Juxtaposition of two such action potentials might be expected to create a potential difference during repolarization and generate an excitatory current of a sufficient magnitude to reexcite the fiber with the shorter action potential duration.<sup>18</sup> This phenomenon was postulated in a small strand of Purkinje fibers.<sup>19</sup> However, such a mechanism would be expected to initiate a spontaneous activity, which was not observed in our study. Most likely, a sharp temperature gradient between the cold and warm areas was prevented by an abundant intercoronary collateral communication in canine hearts and by passive heat conduction in the myocardium. Also, electrotonic interaction could have blunted the sharp potential gradients between the areas with long and short MAP durations.<sup>20</sup> The lack of spontaneous ventricular arrhythmia also decreased the probability that arrhythmia was due to an enhanced automaticity of cardiac Purkinje fibers, which could be expected in the warmed myocardium.<sup>14</sup>

The use of a strong stimulus during VPS requires consideration of local reexcitation due to stimulation during the vulnerable period.<sup>21</sup> However, in our study the stimulus strength was not critical, for stimuli of the same or greater strength did not induce ventricular arrhythmia during control, hypothermia, or RWBP alone.

The initiation of ventricular arrhythmia by a single premature stimulus at the sites distal to the site of stimulation favors the mechanism of reentry, or triggered automaticity<sup>22</sup> and we cannot distinguish between these two possibilities.<sup>23</sup> In isolated rabbit atrial tissue, the circus movement tachycardia dependent on the presence of dispersion of refractoriness was due to reentry.<sup>17</sup> In this preparation, premature impulses originating from the site with short refractoriness were blocked at the site with long refractoriness, which was reexcited retrogradely after recovery of its excitability. A similar mechanism could have been present in our preparation because the arrhythmia was induced only by VPS at the site with short MAP duration in the warm area, while the premature impulse elicited by such VPS encountered conduction delay either at the border between the warm and the cold area or in the cold area (figs. 5 and 6). Another observation compati-

ble with reentry was the presence of independent activation fronts at nonadjacent anatomic locations at the onset of arrhythmia (fig. 8).

### Site of Stimulation

Differences in the site of VPS caused important differences in the magnitude of dispersion and in the relative contribution of its two components to the total dispersion. In the presence of critical dispersion, the AT difference became greater during propagation of VPC elicited at the paraseptal site and smaller during propagation of VPC elicited at the lateral site. We attributed the former to a greater conduction delay during propagation of the VPC from an area with a short refractory period toward the area with a long refractory period and the latter to an opposite effect: a more rapid propagation of an impulse from an area with a long refractory period toward the area with a short refractory period.

Because the site of premature stimulation had no significant influence on the MAP duration difference during control or during hypothermia and RWBP, the increase in dispersion during propagation of VPC was due solely to the increase in the AT difference. When this increase was added to the preexisting large MAP duration difference, a critical magnitude of dispersion was achieved. The lack of a comparable increase in the AT difference during stimulation from the site with long MAP prevented such a degree of dispersion. We assume that when the increase in dispersion of repolarization reached a critical level, propagation of premature impulse originating from the area with a short MAP encountered a block in the area with a long MAP and created conditions favorable for reentry. The large dispersion of repolarization creates an environment that facilitates the development of a conduction delay required to induce a sustained arrhythmia.

The critical role of the site of stimulation in arrhythmogenesis is not a new finding. Michelson et al.<sup>24</sup> reported that the inducibility of sustained ventricular tachycardia in a canine model of chronic infarction was dependent on the site of stimulation and attributed these differences to different local properties of excitability and refractoriness. In dogs with thermal lesions, Burgess et al.<sup>4</sup> found that the ventricular fibrillation threshold was lower near the warm site than at a distance from this site, and that the fibrillation threshold was inversely related to the degree of inequality in the time of recovery of excitability. These authors have postulated that "in the presence of an area of short recovery properties, less inequality in time of recovery would be expected if activation were initiated at a distance from that area than if activation were initiated within the area."<sup>24</sup> Our observations support the validity of this formulation.

### Implications

Our animal model of a reproducible, graded and measurable dispersion of repolarization due predominantly to differences in action potential durations permits us to quantitate the arrhythmogenic role of

differences in action potential durations, define the characteristics of arrhythmia, and suggest its possible mechanism. This information may be helpful in the understanding of ventricular arrhythmia assumed to be dependent predominantly on increased dispersion of repolarization. Such a mechanism of arrhythmia has been postulated in patients with long QT syndrome, where myocardial function tends to be normal, conduction disturbances are absent, and the ECG is normal except for the prolonged QT interval and the presence of ventricular arrhythmia.<sup>25, 26</sup> The occurrence of VPCs during inscription of the T wave (the R-on-T phenomenon) in such patients is compatible with increased dispersion of ventricular repolarization.

Ventricular arrhythmias associated with prolonged QT interval are more effectively controlled by ventricular pacing than by antiarrhythmic drugs.<sup>27-29</sup> Assuming that the increased QT interval in this setting reflects an increase in the dispersion of ventricular repolarization, pacing at a faster rate may be expected to decrease the dispersion and thereby prevent or suppress the ventricular arrhythmia. Our observations (fig. 3) validate this assumption and provide the rationale for this approach to therapy. According to Smith and Gallagher,<sup>27</sup> atrial pacing is more advantageous than ventricular pacing in such patients. This may be also explained by our observation that the change from atrial to ventricular pacing resulted in increased dispersion due to the increase in the AT differences.<sup>30</sup> This increase could possibly offset the beneficial effect of a faster rate on the dispersion.

Several investigators<sup>31-33</sup> have emphasized the difficulty of inducing ventricular arrhythmia by programmed ventricular stimulation in patients with long QT syndrome. If our observations are applicable to these patients, the difficulty of inducing ventricular arrhythmia may be due to the inability of finding an appropriate site of stimulation. In most studies, the programmed ventricular stimulation is usually limited to the sites within the right ventricle. Yet, in a few study patients with long QT interval,<sup>32, 34</sup> long MAP and ERPs have been recorded in the right ventricle. Further clinical studies will be needed to explore the relation between the inducibility of arrhythmia and the duration of the refractory period at the site of stimulation in patients with increased dispersion of repolarization.

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