

## **Dispersion of ventricular repolarization and arrhythmia: study of two consecutive ventricular premature complexes**

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**ABSTRACT** The effect of two consecutive ventricular premature stimuli ( $S_1S_2$ ) during atrial pacing on dispersion of repolarization and inducibility of ventricular arrhythmias was studied in 16 dogs under control conditions and in four dogs in the presence of an increased dispersion of repolarization during atrial pacing induced by general hypothermia and regional warm blood perfusion via selective cannulation of the distal branch of left anterior descending coronary artery. Dispersion of repolarization was measured as the maximal difference between the ends of six simultaneously recorded monophasic action potentials (MAPs) from anterior ventricular surface, and consisted of MAP duration difference and activation time difference. Dispersion of repolarization during atrial pacing at control was  $29 \pm 7$  msec (activation time difference  $4 \pm 6$  msec, MAP duration difference  $25 \pm 8$  msec), that after  $S_1$  at paraseptal the site was  $81 \pm 8$  msec (activation time difference  $73 \pm 12$  msec, MAP duration difference  $8 \pm 5$  msec), and that after  $S_1S_2$  was  $148 \pm 27$  msec (activation time difference  $103 \pm 21$ , MAP duration difference  $44 \pm 26$  msec). Neither  $S_1$  nor  $S_1S_2$  induced ventricular arrhythmia. Hypothermia and regional warm blood reperfusion increased dispersion of repolarization during atrial pacing to  $70 \pm 22$  msec (activation time difference  $9 \pm 3$  msec, MAP duration difference  $61 \pm 19$  msec). During hypothermia and regional warm blood reperfusion,  $S_1$  produced a dispersion of repolarization of  $149 \pm 29$  msec (activation time difference  $85 \pm 8$  msec, MAP duration difference  $64 \pm 23$  msec) and did not induce ventricular arrhythmia. However,  $S_1S_2$  at the paraseptal site induced ventricular fibrillation in all four dogs. At the time of induction of fibrillation, the  $S_2$ -induced activation time difference increased while the MAP duration difference decreased. Our results show the following: (1)  $S_1S_2$  of 2 msec duration and up to 10 times diastolic threshold strength does not induce ventricular arrhythmia in normal myocardium, but does induce arrhythmia in the presence of increased dispersion of repolarization during atrial pacing; (2)  $S_1$  does not induce ventricular arrhythmia but facilitates induction of arrhythmia by  $S_2$  by increasing activation time difference distal to the stimulation site; (3) Increased MAP duration difference facilitates induction of ventricular arrhythmia by increasing activation time difference, but is no longer essential in perpetuation of ventricular arrhythmia after the onset of arrhythmia. Our results imply that  $S_1S_2$ , i.e., an equivalent of a ventricular couplet, does not create sufficient MAP duration difference and activation time difference for induction of ventricular arrhythmia in normal ventricular myocardium.

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IN A PREVIOUS STUDY, we have shown that a single ventricular premature stimulus ( $S_1$ ) of 2 msec duration and of up to 40 mA strength applied during atrial pacing did not induce arrhythmia in open-chest

anesthetized dogs.<sup>1</sup> The dispersion of repolarization after the earliest  $S_1$  averaged  $89 \pm 16$  msec on the ventricular surface, and consisted of a  $23 \pm 13$  msec difference in monophasic action potential (MAP) duration and a  $66 \pm 11$  msec difference in activation time. When we increased the dispersion during atrial pacing (basic dispersion) from an average of  $32 \pm 10$  to  $111 \pm 16$  msec,<sup>1</sup>  $S_1$  produced an additional dispersion averaging 75 msec and induced arrhythmia.

In this study, we tested the effect of two consecutive ventricular premature stimuli ( $S_1$  and  $S_2$ ) during atrial pacing. The purpose of this study was to determine the

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magnitude and the components of dispersion induced by  $S_1$  and  $S_2$ , and their relation to the inducibility of the arrhythmia by this procedure, under control conditions and in the presence of increased basic dispersion of repolarization.

## Methods

Studies were done in sixteen open-chest, artificially ventilated mongrel dogs weighing 20 to 33.5 kg, anesthetized with intravenous pentobarbital sodium (30 mg/kg). The heart rate was kept constant after sinus node crush by atrial pacing with rates ranging from 109 to 120 beats/min (average  $114 \pm 7$ ). The details of the method have been previously described.<sup>1,2</sup> Six suction electrodes were applied to record MAPs at the following locations: (1) on the anterior surface of the right ventricle, (2) on the anterior surface of the left ventricle between the second diagonal branch and the distal branch of the left anterior descending coronary artery (LAD), (3) on the anterior surface of left ventricle between the first and the second diagonal branches of the LAD, (4) on the anterior surface of the left ventricle either medial or lateral to the first diagonal branch of the LAD, and (5) and (6) on the anterolateral surface near the obtuse margin of the left ventricle. The interelectrode distance was 2 to 4 cm between electrodes at sites 1 and 2 and 1 to 2 cm between the remaining electrodes. Local electrograms were recorded with six bipolar plunge electrodes placed at subepicardial locations within 5 mm of the sites of MAP recording. The signals were recorded with a Gould universal preamplifier and amplifier (Model 13-4614-56); the frequency response was set at 0.05 to 1 kHz for MAPs, 30 to 300 Hz for local electrograms, and 0.05 to 300 Hz for the electrocardiogram. The electrograms were recorded simultaneously with the MAPs and an electrocardiographic orthogonal Y lead of the system designed for the dog by McFee and Parungao<sup>3</sup> with Gould Brush 2800 and Honeywell 1858 fiberoptic recorders at paper speed of 200 mm/sec.<sup>1</sup> The criteria for acceptance of the MAPs and the methods of measuring MAP duration and activation time were described previously.<sup>1,2,4,5</sup>

For pacing and programmed premature stimulation, one bipolar pacing electrode was attached to the right atrium and two electrodes were attached to the left ventricle, one within 5 mm of electrode 2 (paraseptal side) and the other within 5 mm of electrode 6 (lateral site). The stimulus during atrial pacing was a rectangular pulse of 2 msec duration and of two times diastolic threshold strength. Programmed ventricular premature stimulation was performed during atrial pacing by applying a single premature stimulus ( $S_1$ ) to one of the two (paraseptal or lateral) stimulation sites. A premature stimulus of two times diastolic threshold scanned diastole at intervals decreasing by 10 to 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 premature stimulation was repeated, scanning early diastole at intervals decreasing by 10 msec. The procedure was then repeated with progressively stronger stimuli of six, eight, and 10 times diastolic threshold strength. After the completion of this program,  $S_1$  of two times diastolic threshold was applied at the paraseptal site at a coupling interval 10 msec longer than ERP. Keeping this stimulation site as well as the strength and the coupling interval of  $S_1$  constant, a second premature stimulus ( $S_2$ ) was applied and the scanning procedure was repeated at each of the two stimulation sites. The threshold of diastolic excitability of the ventricle measured  $0.07 \pm 0.02$  mA at the paraseptal site and  $0.10 \pm 0.13$  mA at the lateral site ( $p = \text{NS}$ ), and remained stable throughout each experiment.

In four of 16 dogs the basic dispersion of repolarization was

increased by altering action potential duration with a combination of general hypothermia and selective perfusion of a branch of the LAD with heated blood (regional warm blood perfusion).<sup>1</sup> The blood was cooled with ice water to  $30^\circ$  to  $31^\circ$  C, measured in the left atrium, and warmed to  $39^\circ$  to  $40^\circ$  C, measured at the outlet of the shunt before entering the LAD. This temperature range was selected to introduce an increase basic dispersion of repolarization at a lower level than the previously established critical value for induction of arrhythmia by  $S_1$  alone.<sup>1</sup> Programmed premature stimulation was performed after hypothermia and regional warm blood perfusion by the protocol described above. The threshold of diastolic excitability of the ventricle in this group of dogs measured  $0.08 \pm 0.03$  mA at the paraseptal site and  $0.07 \pm 0.03$  mA at the lateral site ( $p = \text{NS}$ ) and remained stable throughout each experiment.

Dispersion of repolarization was measured directly as the greatest temporal difference between the ends of simultaneously recorded MAPs. Each value of dispersion could result from MAP duration difference alone, activation time difference alone, or added contributions of both. A negative contribution of activation time or MAP duration difference means that at the site of maximum dispersion, the activation time, or the MAP duration difference detracted from the difference created by one of the other component. In the earlier studies, we have shown that under these experimental conditions the dispersion of repolarization faithfully reflects the dispersion of recovery of excitability.<sup>1,2</sup> The basic dispersion refers to the dispersion of repolarization during atrial pacing, and the premature dispersion to that during  $S_1$  or  $S_2$  premature stimulation. The magnitude of the premature dispersion changed with changing coupling interval. The results reported are the maximum values obtained during each scanning procedure. In those experiments in which  $S_2$  induced ventricular fibrillation, ventricular arrhythmia leading to fibrillation started before completion of the preceding repolarization; this prevented accurate measurement of the MAP duration difference and the maximum dispersion. In these experiments, we measured the maximum dispersion and its two components in the ventricular premature complex induced by the earliest  $S_2$  that caused no arrhythmia.

The statistical probability of differences between means was calculated with paired  $t$  test, and by analysis of variance when more than two groups of data were compared.

## Results

**Premature ventricular stimulation ( $S_1$  and  $S_2$ ) in the absence of increased basic dispersion (table 1 and figure 1).** In 16 dogs QRS duration during atrial pacing averaged  $50 \pm 4$  msec (range 45 to 57) and MAP duration averaged  $238 \pm 18$  msec (range 185 to 280). Table 1 shows the dispersion of repolarization and its two components, MAP duration and activation time difference, during atrial pacing and ventricular premature stimulation. The basic dispersion of repolarization averaged  $29 \pm 7$  msec (range 15 to 40) and consisted of  $4 \pm 6$  msec (range  $-5$  to 15) of activation time difference and  $25 \pm 8$  msec (range 10 to 35) of MAP duration difference. The latter represented the difference between an MAP duration of  $250 \pm 16$  msec and one of  $225 \pm 15$  msec. The dispersion induced by  $S_1$  was significantly greater than that during atrial pacing due to the significantly greater contribution of activation time differ-

TABLE 1

Basic and premature dispersion of repolarization and its components at control and during general hypothermia (H) and regional warm blood perfusion (RWBP)

Experimental condition	Pacing type	No. of observations	Dispersion (msec)	AT difference (msec)	MAP duration difference (msec)
Control	Atrial	16	29 ± 7	4 ± 6	25 ± 8
Control	Atrial + VPS-PS	16	81 ± 18	73 ± 12	8 ± 15
Control	Atrial + VPS-PS <sub>1</sub>	16	148 ± 27	103 ± 21	44 ± 26
Control	VPS-PS <sub>2</sub>				
Control	Atrial + VPS-PS <sub>1</sub>	16	112 ± 24	77 ± 19	35 ± 20
Control	VPS-L <sub>2</sub>				
H + RWBP	Atrial	4	70 ± 22	9 ± 3	61 ± 19
H + RWBP	Atrial + VPS-PS <sub>1</sub>	4	149 ± 29	85 ± 8	64 ± 23
H + RWBP	Atrial + VPS-PS <sub>1</sub>	4	123 ± 10	91 ± 3	31 ± 11
H + RWBP	VPS-L <sub>2</sub>				
H + RWBP	Atrial + VPS-PS <sub>1</sub>	4	133 ± 34	109 ± 20	24 ± 21
H + RWBP	VPS-PS <sub>2</sub> (before VF)				
H + RWBP	Atrial + VPS-PS <sub>1</sub>	4	---	138 ± 5	---
H + RWBP	VPS-PS <sub>2</sub> (at induction of VF)				

VF = ventricular fibrillation; AT = activation time; VPS-PS<sub>1</sub> = ventricular premature stimulation with first premature stimulus at the paraseptal site; VPS-PS<sub>2</sub> = ventricular premature stimulation with second premature stimulus at the paraseptal site; VPS-L<sub>2</sub> = ventricular premature stimulation with second premature stimulus at the lateral site.

<sup>a</sup>p < .001; <sup>b</sup>p < .005; <sup>c</sup>p < .01; <sup>d</sup>p < .05.

ence; the contribution of MAP duration difference decreased. The average MAP duration difference of 8 ± 15 msec represented the difference between an MAP duration of 220 ± 19 msec and one of 212 ± 20 msec.

The dispersion induced by S<sub>2</sub> at both the paraseptal site and the lateral site was significantly greater than that induced by S<sub>1</sub> (table 1 and figure 1) due to the significantly greater MAP duration difference at both stimulation sites and the greater activation time difference at the paraseptal site. The average MAP duration difference of 44 ± 26 msec during S<sub>2</sub> stimulation at the paraseptal site represented the difference between an MAP duration of 189 ± 19 msec and one of 145 ± 24 msec. The average MAP duration difference of 35 ± 20 msec during S<sub>2</sub> stimulation at the lateral site represented the difference between an MAP duration of 221 ± 21 msec and one of 186 ± 20 msec.

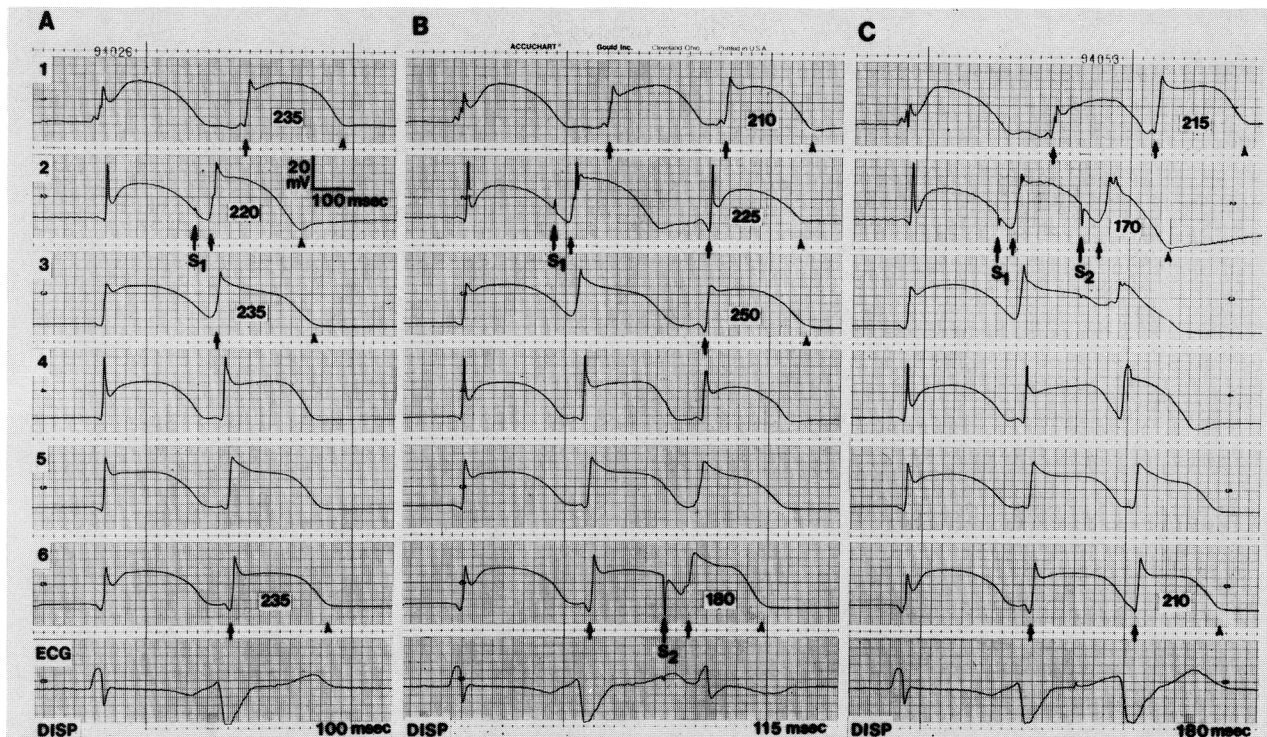
No ventricular arrhythmia was induced by S<sub>1</sub> or S<sub>1</sub> + S<sub>2</sub> at either the paraseptal or the lateral site.

**Premature ventricular stimulation (S<sub>1</sub> and S<sub>2</sub>) in the presence of increased basic dispersion (table 1 and figure 2).** Basic dispersion was increased in four of 16 dogs in which hypothermia and regional warm blood perfusion were used. The magnitude of this dispersion was about 25% to 30% smaller than that critical for induction of arrhythmia by S<sub>1</sub> alone at the paraseptal site in the previous study.<sup>1</sup> In these animals, the control measure-

ments before hypothermia and regional warm blood perfusion were not significantly different from the corresponding control values in the other 12 dogs.

Hypothermia and regional warm blood perfusion caused no significant change in QRS duration (51 ± 5 msec) but increased significantly the basic dispersion of repolarization to 70 ± 22 msec (range 40 to 90) (p < .01). This was due to an increase in the MAP duration difference from 21 ± 10 to 61 ± 19 msec (p < .01) and an insignificant increase in the activation time difference from 4 ± 5 to 9 ± 3 msec (p = NS). The average MAP duration difference represented the difference between an MAP duration of 245 ± 7 msec and one of 184 ± 13 msec. The maximum dispersion induced by S<sub>1</sub> during hypothermia and regional warm blood perfusion was significantly greater than at control (p < .001) due to significantly greater contribution of the MAP duration difference, which averaged 64 ± 23 msec and represented the difference between an MAP duration of 238 ± 13 msec and one of 174 ± 18 msec.

During hypothermia and regional warm blood perfusion, ventricular arrhythmia did not occur spontaneously and was not induced by S<sub>1</sub>. However, S<sub>1</sub> and S<sub>2</sub> induced ventricular arrhythmia when both stimuli were applied at the paraseptal site (figure 2, C). In all four dogs the induced ventricular arrhythmia progressed to



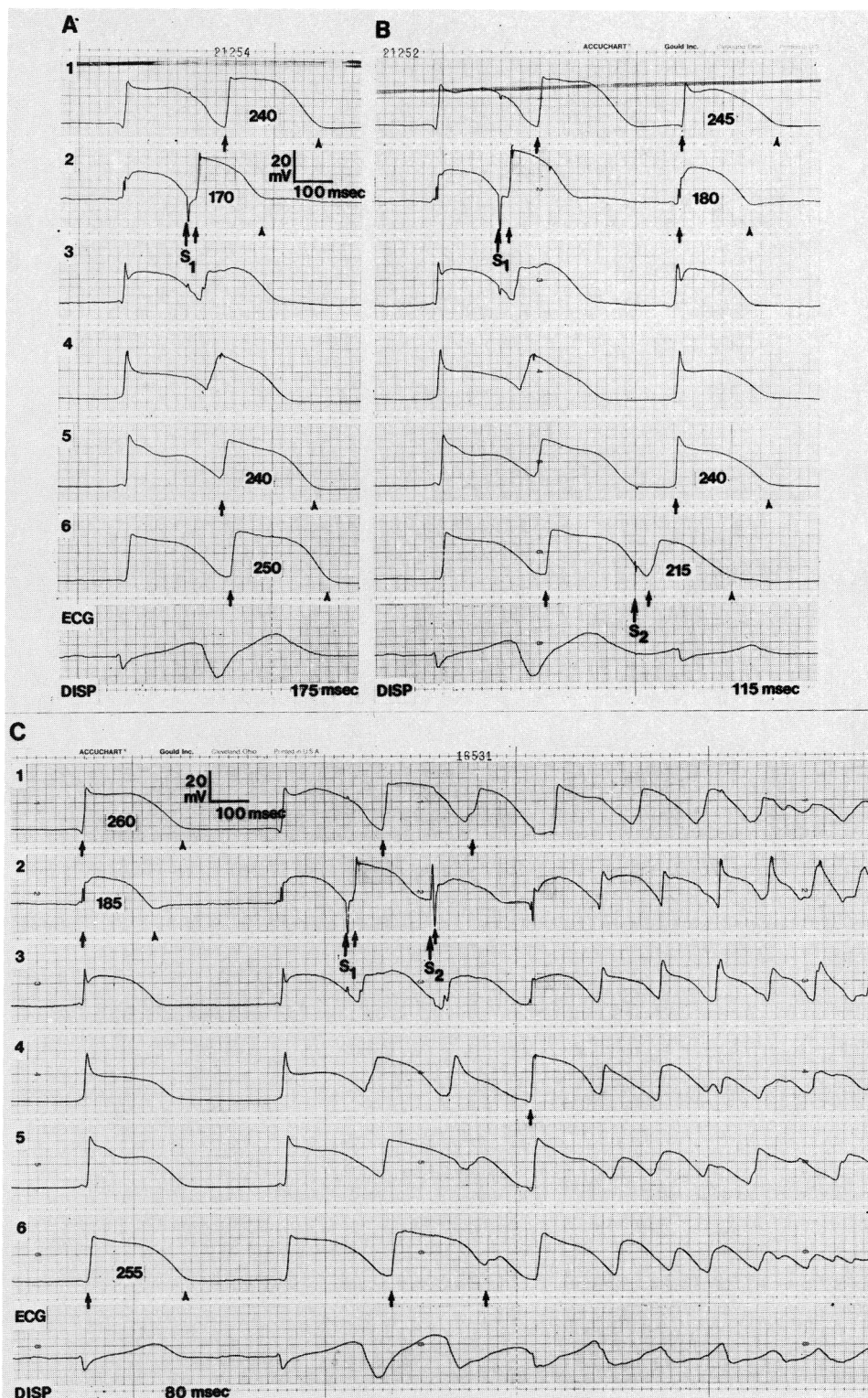
**FIGURE 1.** Dispersion of repolarization induced by  $S_1$  and  $S_2$  in one control dog. Shorter arrows indicate the onset and arrow heads the end of MAPs. Longer arrows indicate the artifacts of  $S_1$  and  $S_2$ . Number within MAPs indicates MAP duration in milliseconds. MAP duration during atrial pacing was 255 msec at recording site 1, 240 msec at site 2, 265 msec at site 3, 245 msec at site 4, 250 msec at site 5, and 255 msec at site 6. The maximum basic dispersion during atrial pacing (15 msec) was between sites 2 and 3, and resulted from an MAP duration difference of 25 msec minus 10 msec activation time difference. In other words, the site of the longer MAP (No. 3) was activated 10 msec earlier than the site of the shorter MAP (No. 2). The maximum dispersion induced by  $S_1$  (A) was between site 2 and 1 and equaled 100 msec, resulting from an MAP duration difference of 15 msec and an activation time difference of 85 msec. B, Two ventricular premature complexes, the first induced by  $S_1$  as in A, and the second induced by  $S_2$  at the lateral site. The maximum dispersion induced by the second premature stimulus was between site 6 and 1 and equaled 115 msec, resulting from an MAP duration difference of 30 msec and an activation time difference of 85 msec. C, Two ventricular premature complexes, the first induced by  $S_1$  as in A, and the second induced by  $S_2$  at the paraseptal site. The maximum dispersion induced by the second premature stimulus was between site 2 and 1 and equaled 180 msec, resulting from an MAP duration difference of 45 msec and an activation time difference of 135 msec. See text.

ventricular fibrillation. The strength of the stimulus that induced the arrhythmia was two times diastolic threshold in two, four times diastolic threshold in one, and six times diastolic threshold in one dog. No arrhythmia was induced in any of the four dogs when  $S_1$  was applied at the paraseptal site and  $S_2$  was applied at the lateral site (figure 2, B).

The maximum dispersion induced by  $S_2$  at the lateral site was  $123 \pm 10$  msec (table 1). It consisted of activation time difference of  $91 \pm 3$  msec and an MAP duration difference of  $31 \pm 11$  msec, which represented the difference between an MAP duration of  $237 \pm 23$  msec and one of  $206 \pm 14$  msec. The maximum dispersion induced by the earliest  $S_2$  that did not induce ventricular fibrillation at the paraseptal site was  $133 \pm 34$  msec. It consisted of an activation time difference of  $109 \pm 20$  msec and an MAP duration difference of  $24 \pm 21$  msec (the difference between an MAP

duration of  $175 \pm 11$  msec and one of  $150 \pm 25$  msec). The premature dispersion and each of its two components at two stimulation sites were not significantly different from one another. The maximum activation time difference of ventricular premature contractions induced by  $S_2$  at the paraseptal site and resulting in ventricular fibrillation was  $138 \pm 5$  msec. This value was significantly greater than the maximum activation time difference induced by  $S_2$  at the lateral site, by  $S_1$  at the paraseptal site ( $p < .001$ ), or by  $S_2$  at either the paraseptal or lateral site under control conditions ( $p < .02$  for paraseptal and  $p < .001$  for lateral site).

During propagation of the ventricular complex induced by  $S_2$ , the earliest activation was recorded at the site of electrode 2 in all four dogs, but during propagation of the first nonstimulated ventricular complex leading to ventricular fibrillation, the earliest acti-



**FIGURE 2.** Dispersion of repolarization of ventricular premature complexes induced by  $S_1$  and  $S_2$  during hypothermia combined with regional warm blood perfusion in one dog. The dispersion during atrial pacing was 80 msec (C), and resulted from an MAP duration difference of 70 msec and an activation time difference of 10 msec. The dispersion induced by the first premature stimulus (A) was 175 msec, and resulted from an MAP duration difference of 80 msec and an activation time difference of 95 msec. The dispersion induced by  $S_2$  at the lateral site (B) was 115 msec, and resulted from an MAP duration difference of 30 msec and an activation time difference of 85 msec. The  $S_2$  at the paraseptal site resulted in ventricular fibrillation (C). The dispersion induced by  $S_2$  at the paraseptal site could not be accurately measured, but the maximal activation time difference between sites 2 and 6 was 135 msec. Symbols are as in figure 1. The arrow below the fifth action potential of site 4 in C indicates the earliest activation of the complex initiating sustained ventricular arrhythmia. See text.



vation was recorded at the site of electrode 3 in two, and at the site of electrode 4 in the other two dogs (figure 2, C).

## Discussion

Our results show that the application of two ventricular premature stimuli during atrial pacing did not induce ventricular arrhythmia under normal conditions but did induce arrhythmia in the presence of increased dispersion of repolarization caused by increased difference in action potential durations. Although we measured the dispersion only on the ventricular surface, we believe that by cooling and warming the blood rather than the cardiac surface, we avoided large transmural temperature gradients, and thus sampled the representative regions with short and long MAPs.

### Mechanism of induced arrhythmia

*Role of  $S_1$  in the presence of an increased dispersion.* Induction of arrhythmia by  $S_1S_2$  required a lesser magnitude of critical basic dispersion than that needed for induction of arrhythmia by a single premature stimulus.<sup>1</sup> This suggests that  $S_1$  introduced additional electrophysiologic disturbances that, in the presence of a less than critical dispersion, facilitated the induction of arrhythmia by  $S_2$ . One of the mechanisms that has been proposed to explain the increased yield of arrhythmia induction with an increasing number of premature stimuli is the shortening of refractoriness that is induced by the first premature stimulus at the site of stimulation, which allows the subsequent premature impulse to be applied earlier and penetrate the reentry circuit.<sup>6</sup>

Although under some conditions the operation of the above mechanism is plausible, our results suggest that in this preparation the role of  $S_1$  in the induction of arrhythmia was not limited to the shortening of refractory period at the site of stimulation. We found that  $S_1$  not only shortened MAP at the site of stimulation but also increased the activation time difference at the sites distal to the site of stimulation and that activation time difference was further augmented by  $S_2$  at the time of induction of arrhythmia. In our preparation of increased dispersion resulting from increased MAP duration difference, the induction of presumed reentrant arrhythmia by  $S_1$  was attributed to conduction block and slow conduction resulting from an activation front reaching the still refractory, or incompletely repolarized regions of myocardium with prolonged MAP.<sup>1</sup> We assume that in this study  $S_1$  had a similar effect. However, because of a less pronounced MAP duration difference  $S_1$  did not induce arrhythmia but created

conditions for completion of reentry of premature impulse induced by  $S_2$ . Such mechanism of arrhythmia induction by  $S_1S_2$  may not be limited to the setting in which the unidirectional block and the slow conduction are attributed to the differences between action potential durations. Mehra et al.<sup>7</sup> proposed a similar mechanism of arrhythmia induction in an infarction preparation in which reentrant arrhythmias were induced by  $S_1S_2$  but not by  $S_1$  alone. The induction of arrhythmia by  $S_2$  was attributed to a long propagation time of the second premature impulse that allowed the dissipation of functional block at the site of reentry. However,  $S_1$  failed to create reentry even though the  $S_1$ -induced impulse reached the site of reentry circuit.<sup>7</sup>

*Role of MAP duration difference.*  $S_1$  decreased MAP duration difference at control but did not change this parameter during hypothermia and regional warm blood perfusion.  $S_2$  increased MAP duration difference at control, but decreased it during hypothermia and regional warm blood perfusion. This confirms our earlier observation that when the basic MAP duration difference is already increased, premature stimulation causes no further increase.<sup>1</sup> The decrease in MAP duration difference induced by  $S_2$  during hypothermia and regional warm blood perfusion can be attributed to the operation of two mechanisms that control the non-cycle length-dependent premature action potential duration in the ventricular myocardium, namely the proximity of the premature action potential to the preceding basic action potential and the duration of the preceding basic action potential.<sup>8</sup> The duration of premature action potential decreases with increasing proximity to the preceding basic potential, but at each diastolic interval (proximity) is proportional to the duration of the preceding basic potential. In our study, these two factors interacted as follows: At short coupling intervals, the proximity of the premature MAP to the basic MAP tended to be similar at all sites (figure 2 A), while at longer coupling intervals the premature MAP tended to be in closer proximity to the long preceding basic MAP than to the short preceding basic MAP (figure 2, B, second premature MAP). In both instances, the absolute shortening of premature MAP was greater after a longer than after a shorter preceding basic MAP. Thus, we found that, in contrast to the increasing activation time difference, the MAP duration difference during  $S_2$  decreased before the induction of arrhythmias. This suggests that in this animal preparation, the increased basic MAP duration difference is needed to delay conduction of the first premature impulse, which in turn leads to further conduction disturbance during propagation of the second premature impulse and initiation

of arrhythmia. It appears that after the initiation of arrhythmia an increased MAP duration difference is no longer needed for its perpetuation.

**Strength of premature stimuli.** The study of Spear *et al.* suggests that a significant increase in the dispersion of recovery of excitability at the site of stimulation occurs when the strength of premature stimuli exceeds 2.0 mA. In our study, the strength of the conditioning  $S_1$  and  $S_2$  that induced ventricular fibrillation was less than 1.0 mA. This suggests that the arrhythmia induced in our study was probably not due to the “destabilizing” effect of  $S_1$  in the vicinity of the stimulation site, a conclusion supported by the finding that the arrhythmia originated at some distance from the site of premature stimulation.

**Site of premature stimulation.** We confirmed the previously established importance of the site of stimulation in the induction of arrhythmia.<sup>1</sup> The arrhythmia was induced only when  $S_2$  was applied at the same site as  $S_1$ , i.e., at a site with short MAP duration. The  $S_2$  applied at this site produced greater activation time difference than that applied at a site different from that of  $S_1$ , i.e., a site with a long MAP duration. This suggests that the second premature impulse propagated more slowly when it originated from the site at which repolarization was completed early.

**Implications of the study.** Ventricular couplet has been classified as high-grade ventricular arrhythmia.<sup>10</sup> A significant association between ventricular couplet and ventricular tachycardia was noted in patients recovering from myocardial infarction,<sup>11, 12</sup> but not in patients without heart disease.<sup>13</sup> Couplets have been found to account for a large proportion of the complex but clinically “benign” ventricular arrhythmias observed during ambulatory electrocardiographic recording in individuals without heart disease.<sup>14, 15</sup> These observations suggest that the prognostic significance of couplets depends on the clinical setting.

It has been shown that in experimental myocardial infarction in dogs, two premature ventricular stimuli of 10 times diastolic threshold or less induce ventricular tachyarrhythmia in the presence of infarction but not under control conditions.<sup>16–18</sup> Our study provides additional experimental evidence that the effect of two consecutive premature stimuli depends on the electrophysiologic homogeneity of the underlying myocardium. Thus, both the clinical and the experimental observations imply that the decisions based on the grading of complexity of ventricular arrhythmia re-

quire the consideration of the characteristics of the population at risk.

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