

Potential by Mild Hypothermia of Ventricular Conduction Disturbances and Reentrant Arrhythmias Induced by Bupivacaine in Dogs

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High concentrations of bupivacaine and profound hypothermia individually cause intraventricular conduction disturbances and reentrant arrhythmias. The effects of the combination of relatively low concentrations of bupivacaine and mild hypothermia are unknown and are the subject of this study. Three groups (n = 10-12) of dogs anesthetized with thiopental-chloralose were treated as follows: group 1, bupivacaine + hypothermia; group 2, bupivacaine alone; group 3, hypothermia alone. Bupivacaine was administered as a 4 mg/kg iv bolus followed by an iv infusion of 0.1 mg · kg⁻¹ · min⁻¹. Hypothermia, i.e., a 4° C reduction in core temperature, was produced by cooling the blood with an extracorporeal circuit. The peripheral ECG was recorded to determine the duration of QRS complexes and the QT interval. Conduction time and effective refractory period (ERP) of ventricular contractile tissue were measured with right ventricular endocavitary electrodes. Measurements were made with the heart paced at 180 beats/min and without pacing. In group 1 dogs, bupivacaine (plasma level, 2.8 ± 0.3 µg/ml) initially caused a prolongation of conduction time and QRS duration, which were further lengthened (approximately doubled) by a temperature decrease of 4° C from baseline. The QT interval and ERP also were increased but to a lesser degree. In dogs in which the effects were most pronounced, rhythm disorders, such as wave burst arrhythmias (most common), premature systoles, ventricular tachycardia, and even ventricular fibrillation, occurred either spontaneously or during pacing. Bupivacaine alone (group 2) increased QRS duration and conduction time significantly, whereas hypothermia alone (Group 3) did not cause changes in any conduction variables. In neither group were dysrhythmias observed. Thus, the combination of moderate bupivacaine concentrations and 4° C hypothermia cause significant cardiac arrhythmias. These results may explain the occasional cardiac disorders that have occurred during apparently uncomplicated regional anesthesia with this agent. (Key words: Anesthetics, local: bupivacaine. Heart, arrhythmias: ventricular conduction. Hypothermia.)

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BUPIVACAINE has an inhibitory effect on ventricular conduction,^{1,2} and at high plasma concentrations (6.0-8.0 µg/ml) may cause life-threatening dysrhythmias.^{3,4} These dysrhythmias, which may be observed after accidental intravascular injection, normally do not occur at the lower bupivacaine concentrations (1.0-1.5 µg/ml) that usually result from the absorption of the drug following local or regional anesthesia. Thus, the occasional occurrence of conduction disorders and arrhythmias in association with usual doses of bupivacaine suggests the association of a factor that may enhance the conduction disturbance.

Hypothermia might be this factor. Certainly, core temperature can decrease in patients who are motionless, are anesthetized in operating rooms in which the temperature is less than 21° C, have open body cavities, and are vasodilated.^{5,6} Although normal ventricular conduction usually is not seriously affected when temperature is decreased by 4° C or less,⁷⁻¹⁰ this may not be the case when conduction previously has been inhibited by bupivacaine. The aim of the current study was to determine if hypothermia potentiates the adverse effects of bupivacaine on ventricular conduction.

Methods

ANIMAL PREPARATION

After approval of the protocol by the institutional animal care committee, 34 mongrel dogs of either sex, weighing between 18 and 28 kg were assigned to one of three groups as follows: 1) bupivacaine-hypothermia (n = 12); 2) bupivacaine-normothermia (n = 12); or 3) hypothermia alone (n = 10). Dogs were anesthetized with sodium thiopental (4 mg/kg) and chloralose (80 mg/kg) injected iv, their tracheas were intubated, and their lungs were mechanically ventilated with a Bird Mark VIII® respirator delivering an air-oxygen mixture (40% and 60%, respectively). Arterial blood gas tensions and pH were measured approximately every 20 min, and values were maintained in the normal range by modifying ventilator settings.

Mean arterial blood pressure was measured directly using a catheter inserted percutaneously into the right femoral artery and connected to a Statham® transducer

TABLE 1. Mean (\pm SE) of the QRS Duration, Conduction Time, Sinus Rate, QT Interval, Ventricular ERP and MAP for Group 2 (bupivacaine–normothermia) Dogs

	Control	Time Period and Temperature				
		0–60 min 39° C	65 min 39° C	70 min 39° C	80 min 39° C	90 min 39° C
QRS duration (ms)	53 \pm 3	69 \pm 4*	69 \pm 4*	70 \pm 3*	70 \pm 3*	70 \pm 4*
Conduction time (ms)	30 \pm 2	44 \pm 3*	45 \pm 3*	45 \pm 3*	45 \pm 3*	46 \pm 3*
Sinus rate (beats/min)	159 \pm 4	156 \pm 5	155 \pm 5	152 \pm 5	146 \pm 6*	142 \pm 6*
QT interval (ms)	192 \pm 8	205 \pm 6*	203 \pm 8	204 \pm 10	207 \pm 11	214 \pm 12*
Ventricular ERP (ms)	142 \pm 5	169 \pm 5*	172 \pm 5*	175 \pm 5*	175 \pm 3*	175 \pm 3*
MAP (mmHg)	146 \pm 6	132 \pm 8*	127 \pm 7*	123 \pm 8*	120 \pm 7*	108 \pm 8*

* $P < 0.05$.

and a Narcotrace® 80 polygraph. Body temperature was measured with an electronic esophageal thermometer. Initially, temperature was maintained at 39° C using an infrared heater placed at a variable distance from the animal. Hypothermia was induced with an extracorporeal circuit, equipped with a peristaltic pump and a heat exchanger, and connected to the left femoral artery and vein with 10-mm catheters.

ELECTROPHYSIOLOGIC RECORDINGS

A surface electrocardiogram (lead II) was obtained using needle electrodes introduced under the skin of each leg and connected to an Elema-Schonander® electrocardiograph. Cardiac electrical activity was continuously monitored on a Siemens® EM 531 oscilloscope and recordings were made to measure the duration of the QRS and QT intervals during periods of normal sinus rhythm.

The ventricles were intermittently paced with a 6F Plastimed Elecath® electrode, introduced percutaneously into the right jugular vein and advanced centrally to the base of the right ventricle, just beneath the tricuspid valve. The electrode was connected to a Racia® stimulator, which delivered square wave stimuli of 1.5 mA intensity (*i.e.*, three times threshold intensity) and 5 ms duration at a rate of 180 beats/min. Pacing was employed because hypothermia reduces the sinus rate, thereby influencing the duration of the QRS and QT intervals, particularly when conduction in ventricular fibers is impaired by drugs, such as bupivacaine.^{4,11–13}

During pacing conduction time was measured in ventricular contractile fibers using a 6F USCI bipolar recording electrode, which had been introduced percutaneously into the right femoral vein and advanced to the apex of the right ventricle. This electrode was connected to an electrocardiograph lead designed to record His bundle potentials. The stimulating electrode also was used for determination of the effective refractory period (ERP) in ventricular muscle, using the extrastimulus method.¹⁴

EXPERIMENTAL PROTOCOL

Animals in each of the groups were treated as follows: Group 1 dogs (bupivacaine–hypothermia) received a 4 mg/kg dose of bupivacaine hydrochloride (Marcaine® Roger Bellon) iv followed by an iv infusion of 0.1 mg·kg⁻¹·min⁻¹ throughout the experiment. After allowing 50–60 min for a steady state to be achieved, the extracorporeal circuit was opened and core temperature of the animals was lowered from 39° C to 35° C within approximately 30 min. The decrease in temperature was limited to 4° C because this degree of hypothermia often occurs in clinical settings. Group 2 dogs (bupivacaine–normothermia) were treated as were those in group 1 except that the blood was circulated but not cooled in the extracorporeal circuit. The extracorporeal circuit was opened only after 50–60 min of bupivacaine infusion and the experiment was prolonged for 30 min so that measurements could be made at the same time as in group 1 (table 1). Group 3 dogs (hypothermia alone) did not receive bupivacaine but were otherwise treated as were those in group 1. Thus, there was a 50–60 min observation period, corresponding to the bupivacaine infusion period for groups 1 and 2, and measurements were made between 60 and 90 min (table 2).

Arterial blood samples were obtained to measure bupivacaine levels each time electrophysiologic measurements were made, *i.e.*, at the end of the steady state period and each time the temperature decreased 1° C (approximately 5, 10, 20, and 30 min after the onset of the hypothermia period). A high performance liquid chromatography method was used with a limit of sensitivity of 20 μ g/l and a coefficient of variation of 4.2% over the concentration range of 0.10–5.00 μ g/l.¹⁵

STATISTICS

Two-way (group and temperature) repeated measures analysis of variance (ANOVA) was used to determine if

TABLE 2. Mean (\pm SE) of the QRS Duration, Conduction Time, Sinus Rate, QT Interval, Ventricular ERP, and MAP for Group 3 (hypothermia alone) Dogs

	Control 39° C	Time Period and Temperature			
		65 min 38° C	70 min 37° C	80 min 36° C	90 min 35° C
QRS duration (ms)	52 \pm 2	53 \pm 2	53 \pm 2	53 \pm 2	53 \pm 2
Conduction time (ms)	32 \pm 1	32 \pm 1	33 \pm 1	33 \pm 1	33 \pm 1
Sinus rate (beats/min)	159 \pm 5	158 \pm 5	157 \pm 5	149 \pm 5*	146 \pm 5*
QT interval (ms)	209 \pm 10	202 \pm 9	202 \pm 8	210 \pm 10	252 \pm 7*
Ventricular ERP (ms)	148 \pm 4	149 \pm 4	150 \pm 4	151 \pm 4	151 \pm 4
MAP (mmHg)	137 \pm 4	135 \pm 4	134 \pm 4	131 \pm 3*	127 \pm 3*

* $P < 0.05$.

there were treatment-related differences in electrophysiologic variables. When differences were found with ANOVA, Dunnett's test was used to determine where the differences lie. $P < 0.05$ was considered statistically significant.

Results

Four dogs died before the end of the study. Two in group 1 died as a result of ventricular fibrillation shortly after the loading dose was administered and the infusion had been started but before hypothermia was instituted. In pilot studies, we have measured plasma bupivacaine levels above 4–5 μ g/ml at this time. One dog in group 2 experienced profound hypotension 2–3 min after the bolus injection of bupivacaine and died shortly thereafter. A second group 2 dog died following hemorrhage during placement of vascular catheters. Data from these animals were excluded from the study.

GROUP 1: BUPIVACAINE-HYPOTHERMIA

Bupivacaine (plasma level, $2.8 \pm 0.3 \mu$ g/ml; mean \pm SEM) clearly depressed intraventricular conduction at 39° C; duration of the QRS complexes increased from 48 ± 3 to 64 ± 3 ms ($P < 0.01$; fig. 1). During the remainder of the experiment the plasma bupivacaine level was essentially stable, not exceeding a mean value of 3.2 μ g/ml. However, the QRS duration gradually increased to 103 ± 5 ms ($P < 0.001$) as core temperature of the animals fell from 39° to 35° C. Similarly, conduction time increased from 32 ± 2 to 48 ± 3 ms ($P < 0.001$) following bupivacaine administration and then to 107 ± 7 ms ($P < 0.001$) with hypothermia (fig. 1). Thus, hypothermia enhanced the inhibitory effect of bupivacaine on intraventricular conduction. The increase in both variables was temperature-dependent, increasing as hypothermia developed. The increase in QRS duration was even more notable because it occurred despite a concomitant bradycardia (154 ± 7 to 112 ± 6 beats/min; fig. 2). Rate-de-

pendent increases also occurred in the QT interval (171 ± 11 to 246 ± 14 ms, $P < 0.001$) and in the ERP of ventricular contractile fibers (161 ± 4 to 200 ± 3 ms, $P < 0.001$; fig. 3).

Mean arterial blood pressure was relatively unaffected by bupivacaine treatment at 39° C (129 ± 5 to 121 ± 5 mmHg) and did not decrease significantly with hypothermia until there was a 2° C fall in temperature ($P < 0.05$; fig. 4). However, as temperature decreased further, there was a more pronounced decrease of blood pressure to 82 ± 8 mmHg ($P < 0.001$).

Disorders in automaticity typical of bupivacaine intoxication were observed in six dogs when conduction time increased by 150–200%. They developed spontaneously in one dog and were triggered by pacing in the other five. Ventricular fibrillation often followed rapidly after the onset of rhythm disorders, which included wave burst arrhythmias (most commonly observed; fig. 5), premature systoles, or ventricular tachycardia.

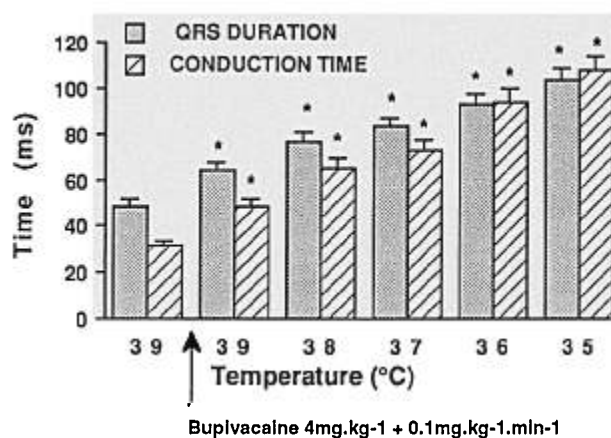


FIG. 1. QRS duration and conduction time in ventricular fibers in group 1 (bupivacaine + hypothermia) dogs ($n = 10$). There was a significant increase in both values as temperature decreased. Values shown are the mean \pm SE. * $P < 0.05$.

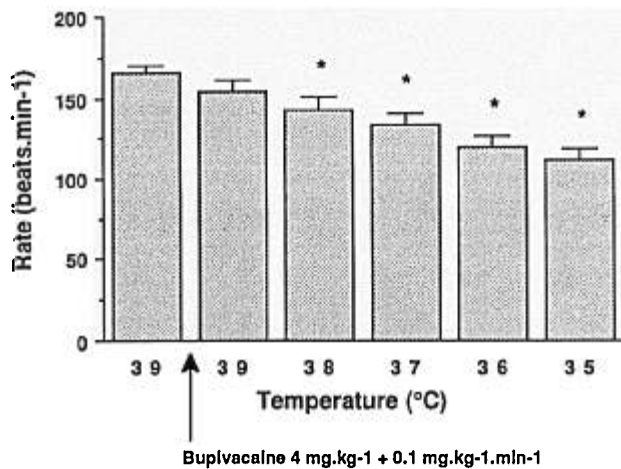


FIG. 2. Sinus rate in group 1 (bupivacaine + hypothermia) dogs ($n = 10$). There was a significant decrease as temperature decreased. Values shown are the mean \pm SE. * $P < 0.05$.

GROUP 2: BUPIVACAINE (NORMOTHERMIA)

The effects of bupivacaine prior to opening the extracorporeal circuit were similar to those observed in group 1. After extracorporeal circulation was instituted, QRS duration, conduction time, ERP, and QT intervals remained unchanged (table 1). The somewhat longer QT interval at 90 min was associated with a slowing of heart rate (from 156 ± 5 to 142 ± 6 beats/min; $P < 0.05$). Mean arterial blood pressure decreased (from 132 ± 8 to 108 ± 8 mmHg; $P < 0.05$) during the last 5 min of the experiment; however, this decrease was less marked than that seen in group 1 during hypothermia.

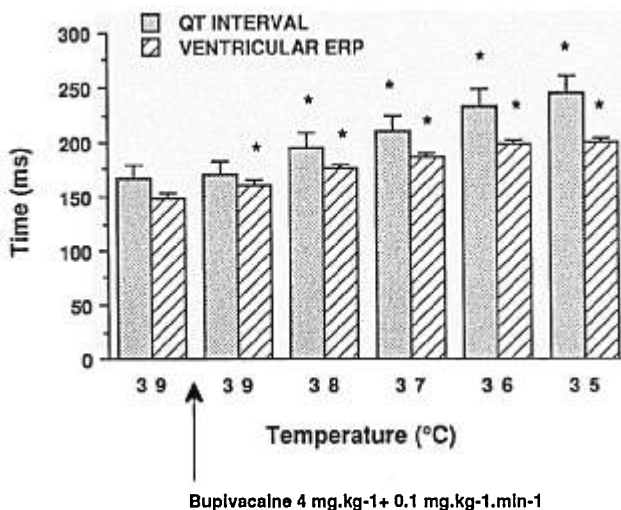


FIG. 3. QT interval and ventricular ERP in group 1 (bupivacaine + hypothermia) dogs. There was a significant increase as temperature decreased. Values shown are the mean \pm SE. * $P < 0.05$.

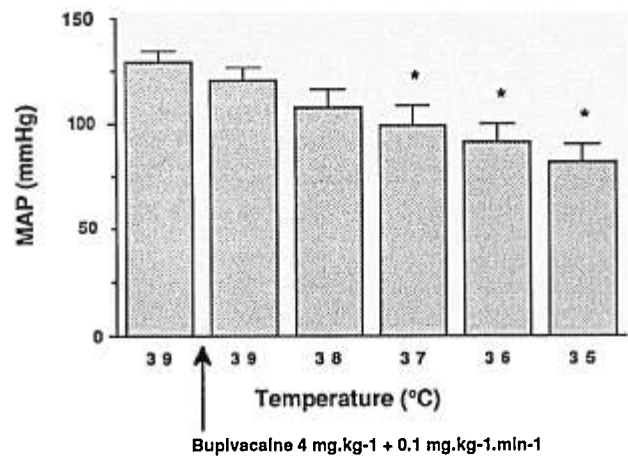


FIG. 4. Mean arterial blood pressure in group 1 (bupivacaine + hypothermia) dogs ($n = 10$). Values shown are the mean \pm SE. * $P < 0.05$.

GROUP 3: HYPOTHERMIA ALONE

Hypothermia to 35°C resulted in minimal changes in QRS duration and ERP (table 2). The increase in QT interval from 209 ± 10 ms to 252 ± 7 ms ($P < 0.05$) was associated with a decrease in sinus rate from 159 ± 5 to 146 ± 5 beats/min ($P < 0.001$). The time course of blood pressure changes was similar to those in group 1, *i.e.*, not significantly different from control at 37°C (137 ± 4 mmHg) but decreasing to 131 ± 3 and 127 ± 3 ($P < 0.01$) at 36° and 35°C , respectively.

Discussion

The combined effects of bupivacaine and hypothermia (group 1) were to prolong depolarization of the ventricular contractile tissue. This was demonstrated by the significant increases in QRS duration and conduction time. These changes were major despite plasma bupivacaine levels of only $2.8 \pm 0.3 \mu\text{g/ml}$ †† and a mild degree of hypothermia (4°C). In contrast, when bupivacaine was administered under normothermic conditions (group 2), no changes in QRS duration and conduction time occurred beyond those initially caused by the drug. Hypothermia alone (group 3) did not result in significant changes. The prolongation of ventricular depolarization was to a large extent responsible for the lengthening of ERP,^{16,17} which increased to a lesser degree than did conduction time or QRS duration. Thus, a 4°C decrease in temperature, which by itself is devoid of adverse effects on intraventricular conduction (QRS duration, conduction time, and ERP), significantly potentiates the depression caused by bupivacaine.

†† Usual plasma bupivacaine levels following regional anesthesia are approximately $1 \mu\text{g/ml}$; they approach $2 \mu\text{g/ml}$ after intercostal nerve block.

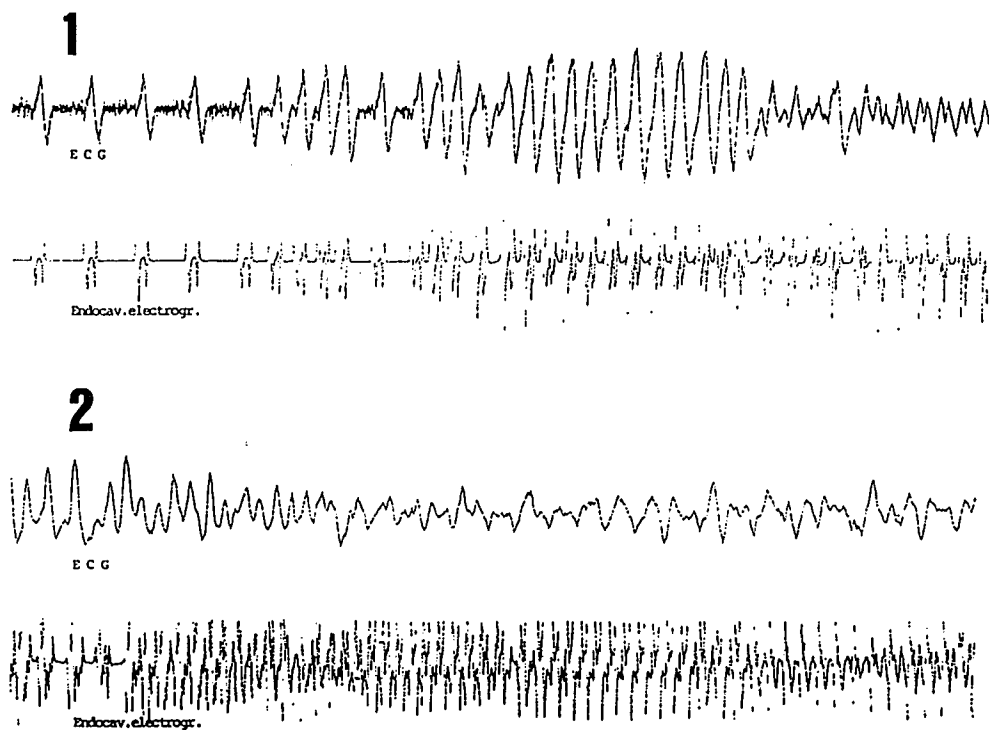


FIG. 5. Rhythm disorders induced by bupivacaine + hypothermia in group 1 dogs, when conduction time in ventricular contractile fibers increased by 150–200%. Strip 2 is the continuation of strip 1.

Treatment with bupivacaine (group 2) and hypothermia (group 3) individually resulted in only slight decreases in heart rate. However, in combination, they caused a 30% decrease in heart rate, which was associated with a prolongation of the QT interval. Blood pressure initially was not affected by the administration of bupivacaine. However, it declined toward the end of the study, probably due to the effects of extracorporeal circulation in all groups (*i.e.*, release of vasodilator substances from erythrocytes, platelets, plasma proteins, and variations in plasma volume) combined with hypothermia in groups 1 and 3.

It is conceivable that hypotension contributed to cardiac toxicity by reducing bupivacaine clearance. However, this is unlikely because the degree of hypotension was moderate (insufficient to appreciably decrease hepatic or renal blood flow) and its duration was brief. This view is supported by the lack of a major increase in mean plasma bupivacaine levels (2.8 to 3.2 $\mu\text{g}/\text{ml}$) as the experiment progressed. The relative stability of plasma bupivacaine concentrations also mitigates the possibility that lowering core temperature inhibited drug metabolism, thus resulting in enhancement of toxic effects. Hypothermic inhibition of metabolic processes has been reported with other drugs.^{18,19} However, this probably requires a decrease in temperature of more than 4° C and of longer duration than occurred in the present study.

Because enhancement of the cardiac effects of bupivacaine by hypothermia cannot be explained by pharmacokinetic changes, they probably depend on pharma-

codynamic mechanisms. Indeed, decreases in temperature of 5–6° C, or more, cause impairment of electrical activity in ventricular fibers,^{7–10} as does administration of bupivacaine.^{3,4} The hypothermic effect is represented electrocardiographically by the J waves that appear near the end of the QRS deflection and widen them.²⁰ With progressive hypothermia widening increases and is associated with a prolongation of the QT interval. This widening is greater than what would be expected from the concurrent bradycardia, which usually occurs at this time and is linked to the lengthening of ERP.^{21–23}

It is likely that the delay in ventricular depolarization caused by hypothermia is increased by the prior administration of bupivacaine, a drug that selectively blocks sodium channels.^{12,13} The latter plays a fundamental role in depolarization of ventricular fibers, the most contractile and most polarized of the cardiac fibers.^{24,25} However, hypothermia only influences transmembrane sodium potentials indirectly, *i.e.*, through a decrease in active ion transfer. These effects are secondary to the reduction in cellular oxidative processes that provide energy for the ion pumps.²⁶ The Van't Hoff (so called Q10) effect, which describes an exponential relationship between changes in temperature and changes in the equilibrium constant for a chemical reaction, can be applied to describe aerobic reactions in intact organisms. Each 7–10° C decrease in core temperature results in a 50% reduction in oxygen consumption.^{27,28} The difference in sodium concentration between intracellular and extracellular fluid is thus di-

minished, as is the resting membrane potential. Both factors give rise to a reduction in passive ion fluxes, primarily of sodium, in ventricular contractile fibers. This reduction is particularly marked when sodium conductance previously has been decreased by a drug, such as bupivacaine,^{12,13} shifting the Weidmann curve (relationship of depolarization to the degree of polarization) to the right. Accordingly, depolarization is slowed and conduction time lengthened to a major extent. Action potential duration and ERP, which are predominantly governed by repolarization, are affected to a much lesser extent.

Our results, *i.e.*, a progressive delay in ventricular conductivity with decreasing temperature accompanied by a lesser prolongation of ERP, can explain the spread of excitation in myocardial tissue that results in the triggering and perpetuation of reentrant arrhythmias.^{29,30} Such arrhythmias have been reported in patients during the course of profound hypothermia (<30° C),⁶⁻⁹ and also were seen in the current study with bupivacaine plus mild hypothermia (35° C) when conduction time was prolonged by at least 150–200%. Given the constraints inherent in extrapolating the results of animal experiments to clinical practice, we wish to raise the possibility that life-threatening conduction disorders may occur with bupivacaine in the presence of hypothermia at plasma concentrations nearer to those reported in clinical circumstances than those usually regarded as toxic.

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