

# Enhancement by Hyponatremia and Hyperkalemia of Ventricular Conduction and Rhythm Disorders Caused by Bupivacaine

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Intraventricular conduction disorders and reentrant arrhythmias in dogs can be produced by high plasma bupivacaine concentrations. The authors' aim was to determine if these conduction disturbances also occurred at moderate plasma bupivacaine concentrations (2.2–3.7 µg/ml) when in association with other factors which affect intracardiac conduction, such as hyponatremia and hyperkalemia. Thus, duration of the QRS complex, ventricular conduction time, and effective refractory period (ERP) was measured during ventricular pacing at 180 beats per min in 46 anesthetized, closed-chest dogs separated into five treatment groups as follows: group I, an iv bolus of 4 mg/kg of bupivacaine plus an infusion of 0.1 mg·kg<sup>-1</sup>·min<sup>-1</sup> of bupivacaine followed in 50–60 min by 10 ml·kg<sup>-1</sup>·min<sup>-1</sup> of 1.5% glycine iv to produce dilutional hyponatremia; group II, 1.5% glycine alone, as above; group III, bupivacaine, as above, followed in 50–60 min by 0.05 mmol·kg<sup>-1</sup>·min<sup>-1</sup> of KCl iv to produce hyperkalemia; group IV, KCl alone, as above; and group V, bupivacaine, as above, except that the duration of infusion was 90 min. QRS duration and ventricular conduction time, which were prolonged approximately 33% and 61%, respectively, by bupivacaine alone were additionally prolonged 29% and 44%, respectively, when serum sodium concentration was lowered to 114 mmol/l and potassium concentration was raised to 7.7 mmol/l. The combinations of bupivacaine and hyponatremia, and bupivacaine and hyperkalemia tended to increase ERP more than did bupivacaine alone, although these changes were not statistically significant. Wave burst arrhythmias and episodes of ventricular tachycardia occurred spontaneously or were triggered by pacing in those dogs in which conduction time was most prolonged. The authors conclude that the effects of hyponatremia and hyperkalemia on cardiac conduction, when superimposed on the effects of moderate plasma concentrations of bupivacaine, may result in severe or even fatal cardiac arrhythmias in dogs. (Key words: Anesthetics, local: bupivacaine. Heart, arrhythmias: ventricular conduction. Ions, potassium: hyperkalemia. Ions, sodium: hyponatremia.)

DYSRHYTHMIAS have been reported in patients following regional anesthesia with bupivacaine<sup>1,2</sup> and severe, even fatal intraventricular conduction disturbances and reen-

trant arrhythmias have been induced in experimental animals by bupivacaine infusion.<sup>3–5</sup> These experimentally induced dysrhythmias have been attributed to the direct effects of high plasma concentrations of bupivacaine on ventricular conduction.<sup>6,7</sup> We wondered if the clinical dysrhythmias might be due to the cardiac electrophysiologic effects of low plasma sodium or high plasma potassium concentrations superimposed upon the conduction effects of more moderate concentrations of bupivacaine. We considered this possibility because ventricular conduction is related to gating of sodium channels, which is affected by the transmembrane sodium gradient, and to the resting membrane potential of cardiac muscle, which is primarily governed by intracellular and extracellular potassium concentrations.<sup>8,9</sup>

The effect of abnormal sodium and potassium concentrations on cardiac rhythm during regional anesthesia with bupivacaine is of more than hypothetical interest. Bupivacaine is used in relatively high dosages for epidural and regional nerve block anesthesia in circumstances in which serum electrolyte abnormalities may be present. For example, hyponatremia as a consequence of massive absorption of hypotonic irrigating solutions is common during transurethral resection of the prostate<sup>10–13</sup> and it often occurs in association with other major operations. Perioperative hyperkalemia is rarer than hyponatremia but is commonly seen in patients with renal failure. Thus, we investigated the effects of hyponatremia and hyperkalemia on ventricular conduction in dogs with bupivacaine concentrations in the range of those that are occasionally encountered clinically.<sup>14,15</sup> If ventricular conduction disorders were aggravated by these electrolyte abnormalities, then regional anesthesia with large doses of bupivacaine might be contraindicated in patients with these disturbances.

## Methods

### ANIMAL PREPARATION

After approval of the protocol by the institutional animal care committee, 46\*\* mongrel dogs of either sex

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\*\* Data from one group I dog and one group III dog which died before the end of the experiment were not included in the analyses (see Results).

weighing 14–24 kg were assigned to one of five groups as follows: I) bupivacaine-hyponatremia ( $n = 11$ ); II) hyponatremia alone ( $n = 10$ ); III) bupivacaine-hyperkalemia ( $n = 11$ ); IV) hyperkalemia alone ( $n = 10$ ); and V) bupivacaine alone ( $n = 4$ ).<sup>††</sup> Dogs were anesthetized with sodium thiopental (4 mg/kg) and chloralose (80 mg/kg) injected iv, following which their tracheas were intubated and their lungs ventilated with a Bird Mark VIII respirator delivering an air-oxygen mixture (40:60%, respectively). Arterial blood gas tensions and pH were checked approximately every 20 min and values maintained in the normal range by modifying ventilator settings. Mean arterial blood pressure (MAP) was measured directly using a catheter inserted percutaneously into a femoral artery and connected to a Statham transducer and a Narcotrace 80 polygraph. Body temperature was carefully monitored with an electronic esophageal thermometer and kept constant at 39° C by means of an infrared heater placed at a variable distance from the animal.

#### ELECTROPHYSIOLOGIC RECORDINGS

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

The ventricles were intermittently paced with a 6-F 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 mA (twice threshold intensity) and 5 ms duration at a rate of 180 beats per min. During pacing, conduction time was measured in ventricular contractile fibers using a 6-F Plastimed USCI bipolar recording electrode that 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 according to the extrastimulus method.<sup>16</sup> In brief, while the ventricles were driven by the stimuli, S1, the characteristics of which are described above, a premature extrastimulus, S2, of the same characteristics as S1 was introduced. The S1-S2 interval was shortened in 10-ms decrements until the extra response

disappeared. The longest coupling interval, S1-S2, was taken as the ERP. To avoid possible artifacts due to repetition of extrastimuli, care was taken not to initiate the extrastimulus before 8–10 S1 stimuli. Thus, the effects of treatment on conduction velocity and ERP could be assessed independent of the indirect influence of variations in stimulation rate.<sup>17,18</sup>

#### EXPERIMENTAL PROTOCOL

Animals in each of the groups were treated as follows:

Group I dogs (bupivacaine-hyponatremia) received a 4 mg/kg iv loading dose of bupivacaine hydrochloride (Marcaïne, Roger Bellon), followed by a 0.1 mg·kg<sup>-1</sup>·min<sup>-1</sup> iv infusion of bupivacaine throughout the experiment. After allowing 50–60 min for a steady state to be achieved, 10 ml·kg<sup>-1</sup>·min<sup>-1</sup> of hypotonic (1.5%) glycine solution was simultaneously infused iv for 5 min.

Group II dogs (hyponatremia alone) received 1.5% glycine solution, as above, but without the prior and the simultaneous administration of bupivacaine.

Group III dogs (bupivacaine-hyperkalemia) received bupivacaine iv, as above, and after 50–60 min when a steady state had been achieved, 0.05 mmol·kg<sup>-1</sup>·min<sup>-1</sup> of potassium chloride was simultaneously infused iv for 30 min.

Group IV dogs (hyperkalemia alone) received potassium chloride solution as above but without the prior and the simultaneous administration of bupivacaine.

Group V dogs (bupivacaine alone) received bupivacaine iv, as above, except the duration of infusion was 90–100 min.

Arterial blood samples were obtained to measure bupivacaine concentrations each time electrophysiologic measurements were made, *i.e.*, at the end of the steady state bupivacaine infusion (50–60 min) and approximately 5, 10, 20, and 30 min after the onset of the glycine and potassium infusions. Measurements were made at least every 10 min in group V dogs. A high performance liquid chromatography method was used with a limit of sensitivity of 20 µg/l and a coefficient of variation of 4.2% over the concentration range of 0.1–5 µg/ml.<sup>19</sup> Plasma sodium and potassium concentrations and osmolality were determined at the same times.

#### STATISTICS

To determine the relationship between plasma sodium and potassium concentrations and electrophysiologic variables, two-way (group and electrolyte concentration) repeated measures analysis of variance was used. When significant differences were found, Sheffe's test was employed to determine where the differences lie. The electrophysiologic effects of bupivacaine in groups I, III, and

<sup>††</sup> This group was added at a later date as an additional control to the groups that received glycine or potassium from minutes 60–90 of the bupivacaine infusion.

V dogs were determined by comparing steady state (50–60 min) values with those obtained prior to bupivacaine administration using Student's *t* test for paired data. *P* < 0.05 was considered significant for all comparisons.

### Results

Two dogs died before the end of the study, one in group I and one in group III. The group I dog died 2–3 min after the bolus injection of bupivacaine as a result of cardiovascular collapse secondary to a rhythm disorder. The group III dog died before the 20th min of the combined bupivacaine-potassium infusion as a result of ventricular fibrillation resistant to electric countershock. Because their studies were incomplete, data from these animals were excluded from the statistical analyses.

#### GROUP I (BUPIVACAINE-HYPONATREMIA)

Mean plasma bupivacaine concentration ranged from  $3.1 \pm 0.4 \mu\text{g/ml}$  ( $\pm\text{SEM}$ ) following the bolus injection to  $2.9 \pm 0.3 \mu\text{g/ml}$  immediately preceding the onset of the glycine infusion. These values were associated with a slowing of ventricular conduction compared with pre-bupivacaine values as evidenced by a 33% increase in QRS duration ( $57.3 \pm 10.6 \text{ ms}$  to  $76.4 \pm 16.9 \text{ ms}$ ; *P* < 0.05) and a 61% lengthening of conduction time ( $35.5 \pm 8.3 \text{ ms}$  to  $57.2 \pm 15.5 \text{ ms}$ ; *P* < 0.05; fig. 1). At the end of the 5-min glycine infusion, bupivacaine concentrations had fallen to  $2.2 \pm 0.3 \mu\text{g/ml}$  and sodium concentrations had decreased from  $147 \pm 2.9 \text{ mmol/l}$  to  $114 \pm 7.1 \text{ mmol/l}$ . Sinus rate slowed by 15% ( $143 \pm 23 \text{ beats per min}$  to  $124 \pm 24 \text{ beats per min}$ ; *P* < 0.05; fig. 2). Despite the

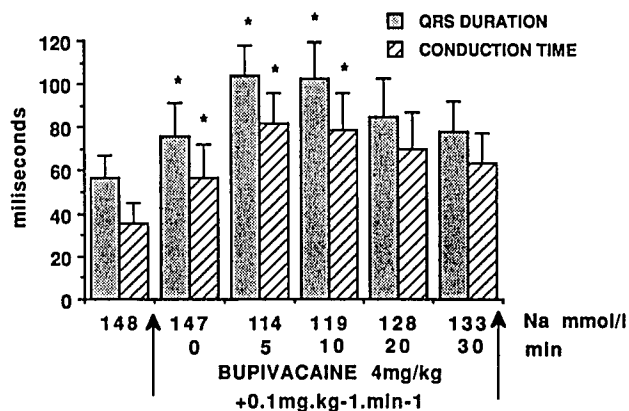


FIG. 1. QRS duration and conduction time in ventricular contractile fibers in group I (bupivacaine-hyponatremia) dogs. The arrows indicate the duration of the bupivacaine infusion. Infusion of hypotonic (1.5%) glycine solution for 5 min beginning at time 0 resulted in a decrease in plasma sodium concentration from 147 mmol/l to 114 mmol/l and a significant increase in both values. At the end of the infusion when hyponatremia abated, conduction returned toward control values. Data are mean values  $\pm$  SEM for ten dogs. \**P* < 0.05.

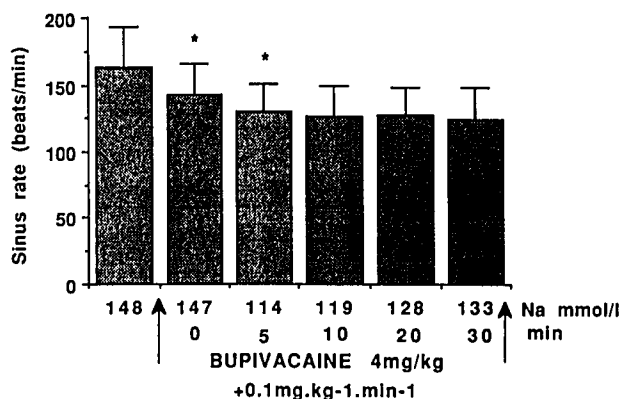


FIG. 2. Sinus rate in group I (bupivacaine-hyponatremia) dogs. The arrows indicate the duration of the bupivacaine infusion. Infusion of hypotonic (1.5%) glycine solution for 5 min beginning at time 0 resulted in a decrease in plasma sodium concentration from 147 mmol/l to 114 mmol/l and a significant decrease in sinus rate. Data are mean values  $\pm$  SEM for ten dogs. \**P* < 0.05.

decreased bupivacaine concentration, ventricular conduction was further impaired: QRS duration increased an additional 29% to  $98.2 \pm 23.8 \text{ ms}$  (*P* < 0.05) and conduction time increased 44% to  $82.6 \pm 23.5 \text{ ms}$  (*P* < 0.05; fig. 1). During the next 25 min, the plasma sodium concentration increased to  $133 \pm 6.7 \text{ mmol/l}$  while QRS duration and conduction time returned towards preglycine infusion values. Bupivacaine concentration at the end of 30 min was  $2.4 \pm 0.4 \mu\text{g/ml}$ .

The tendency for bupivacaine to prolong ventricular ERP and to reduce MAP was enhanced by hyponatremia but in all instances the increases were not significant. Failure of the glycine infusion to increase MAP is noteworthy as it caused significant hyponatremia, most likely as a result of volume expansion.

Disorders in automaticity typical of bupivacaine intoxication were observed when conduction time was augmented by almost 150%. Wave burst arrhythmias and episodes of ventricular tachycardia were triggered by pacing in five of the ten dogs but they did not last more than a few seconds and they did not result in ventricular fibrillation.

#### GROUP II (HYPONATREMIA ALONE)

Comparison of results from groups I and II dogs suggests that hyponatremia enhanced the effects of bupivacaine on intraventricular conduction. In the absence of bupivacaine, glycine induced a decrease in plasma sodium concentration ( $147 \pm 1.9 \text{ mmol/l}$  to  $115 \pm 5.8 \text{ mmol/l}$ ) which was similar to that seen in group I dogs. This resulted in a nonsignificant 12% increase in QRS duration ( $55.4 \pm 7.8 \text{ ms}$  to  $62 \pm 9.5 \text{ ms}$ ), a small but significant 29% increase in conduction time ( $38.8 \pm 8.9 \text{ ms}$  to  $50$

$\pm 6.4$  ms) and an insignificant reduction in sinus rate from  $174 \pm 28$  beats per min to  $142 \pm 26$  beats per min. The increase in ERP ( $139 \pm 20$  ms to  $147 \pm 22$  ms) was not significant nor was the increase in MAP ( $135 \pm 27$  mmHg to  $141 \pm 27$  mmHg).

#### GROUP III (BUPIVACAINE-HYPERKALEMIA)

The time course of plasma bupivacaine concentrations was similar in groups I and III dogs until the start of the potassium infusion. At that time, instead of the decrease in bupivacaine concentration seen in group I dogs there was an increase from  $2.8 \pm 0.4$   $\mu\text{g/ml}$  to  $3.7 \pm 0.5$   $\mu\text{g/ml}$  at the end of the experiment. However, until potassium concentrations reached  $6.9 \pm 0.3$  mmol/l at the 20th min of infusion, the consequences were minor. By that time, the QRS duration which was lengthened 28% by bupivacaine ( $56.2 \pm 11.1$  ms to  $72.2 \pm 10.6$  ms;  $P < 0.05$ ) had increased a further 20% to  $86.4 \pm 15$  ms ( $P < 0.05$ ) and conduction time, which was lengthened 50% by bupivacaine ( $31.8 \pm 9.4$  ms to  $47.7 \pm 14.8$  ms;  $P < 0.05$ ) had increased an additional 29% to  $61.4 \pm 16.2$  ms (ns; fig. 3). By the time potassium concentration reached  $7.7 \pm 0.6$  mmol/l at 30 min, conduction changes were yet more pronounced: QRS duration had increased a further 14% to  $98.6 \pm 13.4$  ms ( $P < 0.05$ ) and conduction time an additional 30% to  $80 \pm 22.6$  ms ( $P < 0.05$ ). In the absence of pacing, the inhibition of intraventricular conduction was sufficient to induce ventricular fibrillation in one dog. With pacing, conduction time was lengthened an average of 158% in seven other dogs; dysrhythmias including ventricular fibrillation resulted in death in two of these animals. The changes in other variables were

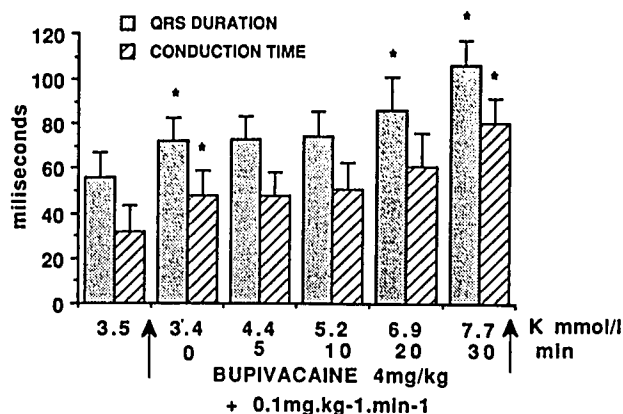


FIG. 3. QRS duration and conduction time in ventricular contractile fibers in group III (bupivacaine-hyperkalemia) dogs. The arrows indicate the duration of the bupivacaine infusion. Infusion of potassium chloride solution from 0–30 min resulted in an increase in plasma potassium concentration from 3.4 mmol/l to 7.7 mmol/l and a substantial increase in both indices of conduction. Data are mean values  $\pm$  SEM for ten dogs. \* $P < 0.05$ .

insignificant throughout the experiment, *i.e.*, sinus rate decreased from  $136 \pm 28$  beats per min to  $127 \pm 27$  beats per min, blood pressure decreased from  $119 \pm 14$  mmHg to  $108 \pm 12$  mmHg, and ERP increased from  $174 \pm 18$  ms to  $189 \pm 18$  ms even by the 20th and 30th min of potassium infusion.

#### GROUP IV (HYPERKALEMIA ALONE)

At plasma potassium concentrations up to  $7.3 \pm 0.7$  mmol/l, QRS duration and conduction time did not change significantly. There also were insignificant increases in sinus rate ( $147 \pm 44$  beats per min to  $158 \pm 34$  beats per min), ERP ( $142 \pm 23$  ms to  $156 \pm 32$  ms) and MAP ( $110 \pm 32$  mmHg to  $112 \pm 29$  mmHg).

#### GROUP V (BUPIVACAINE ALONE)

The peak plasma bupivacaine concentration,  $3.3 \pm 0.4$   $\mu\text{g/ml}$ , was measured 5 min after the loading dose was administered and the infusion had been started. The concentration gradually decreased to  $2.8 \pm 0.4$   $\mu\text{g/ml}$  at 30 min but then remained relatively stable between  $2.5$   $\mu\text{g/ml}$  and  $3.1$   $\mu\text{g/ml}$  during the rest of the experiment. Similarly, QRS duration and ventricular conduction time were stable, decreasing insignificantly from the values at 60 min,  $52.2 \pm 8.4$  ms and  $37.2 \pm 6.2$  ms, respectively, to those at 90 min,  $48.3 \pm 8.8$  ms and  $34.6 \pm 7.4$  ms, respectively. Effective refractory period, 150 ms, and sinus rate, 130 beats per min, were stable throughout the entire experiment. No reentrant arrhythmias occurred during pacing or while measuring ERP.

#### Discussion

In this study, the administration of hypotonic (1.5%) glycine and KCl solutions intensified the ventricular conduction and rhythm disorders caused by moderate plasma concentrations (2.2–3.7  $\mu\text{g/ml}$ ) of bupivacaine. We do not doubt that the effects of the KCl infusion were attributable to hyperkalemia; however, before we ascribe the effects of the glycine infusion to hyponatremia we should consider the other possible consequences it might have had. These include hypervolemia, hypo-osmolality leading to hemolysis and hyperkalemia, and direct glycine toxicity.<sup>20,21</sup>

When viewed in the context of the marked hyponatremia that resulted, it is likely that the glycine infusion in group I dogs resulted in acute hypervolemia; similarly, absorption of glycine during transurethral resection of the prostate often leads to volume overexpansion.<sup>22,23</sup> Based on our clinical experience we would expect to observe cardiovascular signs of volume overload (bradycardia, hypertension, and in extreme cases, congestive heart failure) but rarely would the picture include ventricular

dysrhythmias. Central nervous system signs of water intoxication, *i.e.*, restlessness, confusion, lethargy, convulsions, and coma are usually attributed to hyponatremia superimposed upon hypervolemia. In extreme cases of hypervolemia associated with markedly decreased osmolality, hemolysis might result and this could lead to hyperkalemia. However, in this study, hemolysis was not apparent and plasma potassium concentrations did not increase significantly. Finally, it has been speculated that glycine has a direct toxic effect<sup>11,12</sup> on the central nervous system and possibly on the myocardium as well. There may be some basis for attributing central nervous system toxicity to glycine as its distribution is similar to that of  $\gamma$ -aminobutyric acid, an inhibitory transmitter in the brain; it has been postulated that glycine may be an inhibitory transmitter acting in the spinal cord and brain stem.<sup>24</sup> However, at present, there is no basis for suggesting that glycine is toxic to the myocardium.

Therefore, we believe that hyponatremia in combination with bupivacaine was the factor most likely responsible for the cardiac disturbances that followed infusion of the glycine solution. The effects appeared to be primarily on intraventricular conduction as the hyponatremia-induced changes in sinus rate and in ERP of ventricular fibers were slight. Examination of data from group I dogs indicate that the effects of bupivacaine alone were to produce significant increases in QRS duration and conduction time; group II data show that hyponatremia alone results in a tendency toward the same effects. Together, hyponatremia and moderate concentrations of bupivacaine were at least additive and perhaps potentiated one another. Conduction abnormalities paralleled the change in plasma sodium concentrations, tending to disappear as plasma sodium concentrations returned toward normal. Moreover, it is known from other studies<sup>25</sup> that hyponatremia reverses, at least partially, the untoward effects of bupivacaine on intraventricular conduction.

Intraventricular conduction also was delayed by the combination of hyperkalemia and bupivacaine when potassium concentrations reached 6.8 mmol/l. A further increase in plasma potassium concentration to 7.7 mmol/l caused an additional prolongation in conduction time which at times resulted in serious dysrhythmias. The aggravation of bupivacaine-induced dysrhythmias by the combination of hyperkalemia and acidosis has been previously reported.<sup>4,25-28</sup> Our investigation that reports the effects of hyperkalemia on bupivacaine-altered conduction independent of changes in intracellular potassium and of other biochemical changes that occur in cells during hypoxia is consistent with the results of earlier studies.<sup>29,30</sup> What is new in this study is the use of measurements of QRS duration and ventricular conduction time as indicators of bupivacaine-induced conduction abnormalities. In previous studies, conclusions regarding conduction

were based on changes in sinus node automaticity or in atrioventricular nodal conduction.<sup>26-28,31</sup>

Several additional points are worthy of comment. First, it is unlikely that the enhancement of the cardiac effects of bupivacaine by hyponatremia depended on pharmacokinetic mechanisms. During the glycine infusion there was a 24% decrease in bupivacaine concentrations from 2.9  $\mu$ g/ml to 2.2  $\mu$ g/ml. Thus, dysrhythmias occurred despite a reduction in bupivacaine concentrations. To the contrary, a pharmacokinetic explanation might be partially evoked to explain the conduction effects of the KCl infusion as the mean plasma bupivacaine concentration increased by 32% during the infusion, increasing from 2.8  $\mu$ g/ml to 3.7  $\mu$ g/ml. Also, the lack of dysrhythmias in group V dogs suggests that it is unlikely that conduction disturbances were due to deterioration of the preparation, secondary to prolonged bupivacaine infusion, during the last 30 min of the experiment. It is our impression, however, that intensification of bupivacaine-induced cardiac disorders by hyponatremia and hyperkalemia is a predominantly pharmacodynamic event that is consistent with known electrophysiologic processes. Lowering plasma sodium concentrations leads to a reduction in sodium concentration in the extracellular clefts surrounding myocardial fibers. This results in a reduction in the resting membrane potential and in the intracellular-extracellular sodium concentration difference. These two factors along with sodium permeability<sup>8,9</sup> control depolarization velocity and, therefore, conduction velocity in myocardial fibers. The relationship between the degree of polarization and depolarization velocity is a sigmoid one.<sup>32</sup> When sodium permeability is normal, conduction velocity is unaffected or is only slightly affected by hyponatremia because ventricular fibers are highly polarized, *i.e.*, they respond as if they were at the highest part of the sigmoid-shaped curve that is nearly parallel to the x axis. Bupivacaine blocks sodium channels in the myocardium<sup>33</sup> reducing sodium permeability and shifting the sigmoid-shaped curve to the right and the relationship between the degree of polarization and depolarization velocity to the steep part of the curve. There is some evidence that the inward sodium current also could be depressed by hyperkalemia,<sup>33-35</sup> although potassium ions are thought to be directly involved in repolarization only. In view of their pre-eminent role in polarization of the cells,<sup>8,9</sup> an excess of potassium in extracellular spaces could result in a large decrease in the resting membrane potential, thereby counteracting transmembrane sodium inward current and enhancing bupivacaine effects.

To the extent that animal data can be extrapolated to humans, we believe that if significant intraoperative hyponatremia or hyperkalemia are present (or are likely to occur), anesthetic techniques that might lead to high blood concentrations of bupivacaine, *e.g.*, epidural or brachial

plexus block, should be used with caution. Hyponatremia or hyperkalemia could add to or even potentiate bupivacaine-induced inhibition of intraventricular conduction and result in serious rhythm disorders.

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