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Effects of Bupivacaine and Lidocaine on AV Conduction in the Isolated Rat Heart: Modification by Hyperkalemia

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The intrinsic cardiotoxicities of bupivacaine and lidocaine were examined in the isolated, perfused rat heart. The perfusates contained no protein and were equilibrated with a gas mixture of 95 per cent O_2 and 5 per cent CO_2. Autonomic activity, competitive binding, and postseizure hypoxia and acidosis were absent in this experimental model. The effects of the two local anesthetics were evaluated at normokalemia (5.9 mEq/l) and hyperkalemia (9.0 mEq/l). For normokalemia, the ratio of the potency of bupivacaine to that of lidocaine was 14 for slowing ventricular rate to 50 per cent of control, 6 for slowing atrial rate to 50 per cent of control, and 17 for doubling of the PR interval. The action of bupivacaine to slow ventricular rate was due to an inhibitory effect on both AV conduction and atrial rate. For lidocaine, ventricular slowing was mediated mainly by an inhibition of atrial rate with decreased AV conduction playing a minor role. Hyperkalemia of 9.0 mEq/l had little effect on heart rate or AV conduction in the absence of bupivacaine or lidocaine. It did, however, greatly potentiate the effect of both local anesthetics to slow ventricular rate. For bupivacaine, ventricular slowing to 50 per cent of control during hyperkalemia was accomplished almost entirely via an inhibition of AV conduction, while for lidocaine it occurred because of inhibition of both AV conduction and atrial rate. Regardless of the mechanism, hyperkalemia of this degree increased the ventricular slowing effect of both bupivacaine and lidocaine. (Key words: Anesthetics, local: bupivacaine; lidocaine. Heart: atrioventricular node; AV block; AV conduction; pulse rate. Ions: potassium.)

RECENTLY, de Jong and Bonin[1] reported that although bupivacaine was only twofold more potent than lidocaine for the induction of seizures in mice, animals that seized after bupivacaine injection had disproportionately higher (15-fold) mortality than those that seized after lidocaine. These authors suggested direct cardiotoxicity of local anesthetics at the seizure level because of the preponderance of pallor over cyanosis.

To further compare the intrinsic cardiotoxicity of bupivacaine and lidocaine, we have evaluated the effect of these drugs in the isolated, perfused rat heart. We first compared the effects of bupivacaine and lidocaine at concentrations sufficiently high for both drugs to exhibit marked cardiotoxicity. Secondly, in view of the previously described dependency of lidocaine's cardiotoxic effect on the concentration of extracellular K^+,[2–4] we have compared the cardiotoxicity of relatively low concentrations of bupivacaine and lidocaine in the presence of hyperkalemia.

Materials and Methods

Sixty-four rats (Sprague-Dawley, female, retired breeder) were used. Hearts were excised as soon as adequate anesthesia was established after intraperitoneal injection of thiamylal sodium (about 100 mg/kg). Cannulae (polyethylene tubing, ID 1.40 mm) were placed in the aorta and left atrium. The basal perfusion medium used was a modified Krebs-Henseleit bicarbonate[5] which contained NaCl, 118 mM; KCl, 4.7 mM; $MgSO_4$, 1.2 mM; $NaHCO_3$, 25 mM; KH_2PO_4, 1.2 mM; $CaCl_2$, 2.5 mM; EDTA, 50 μM; and glucose, 11 mM. Potassium ion concentration (5.9 mEq/l) of the basal medium corresponds to the plasma concentration of this ion in rats.[6] All media were equilibrated with a gas mixture of 95 per cent O_2 and 5 per cent CO_2, and the perfusion temperature was 37° C. The spontaneously beating hearts were initially perfused in a retrograde aortic manner (pressure 80 cm H_2O) with the basal medium for a period of about 5 min to wash out the anesthetic and allow recovery from the brief period of global ischemia which occurred during cannulation. This was followed by perfusion in the working heart mode[7] with the same basal medium, and heart function was allowed to stabilize (5–10 min). In the working heart mode, hearts ejected the perfusate entering through the left atrium (reservoir height, 20 cm above the heart) to the height of 80 cm above the heart through the aorta. The ECG was measured with a pair of electrodes placed on the surface of the heart. Aortic pressure was measured with a Statham pressure transducer. All variables were recorded on a Gilson polygraph.

After ECG and aortic pressure for the first control period (*i.e.*, period of perfusion with the basal medium containing 5.9 mEq/l of K^+ and no local anesthetics) were recorded, the effect of various perfusate concentrations of local anesthetics during normokalemia and during hyperkalemia was studied. The concentrations of local anesthetics were: bupivacaine, 1.25, 2.5, 3.75, 5.0, 7.5, 10, 20, and 30 mg/l; and lidocaine, 10, 20, 30, 40, 60, 90, 120, and 150 mg/l. The K^+ con-

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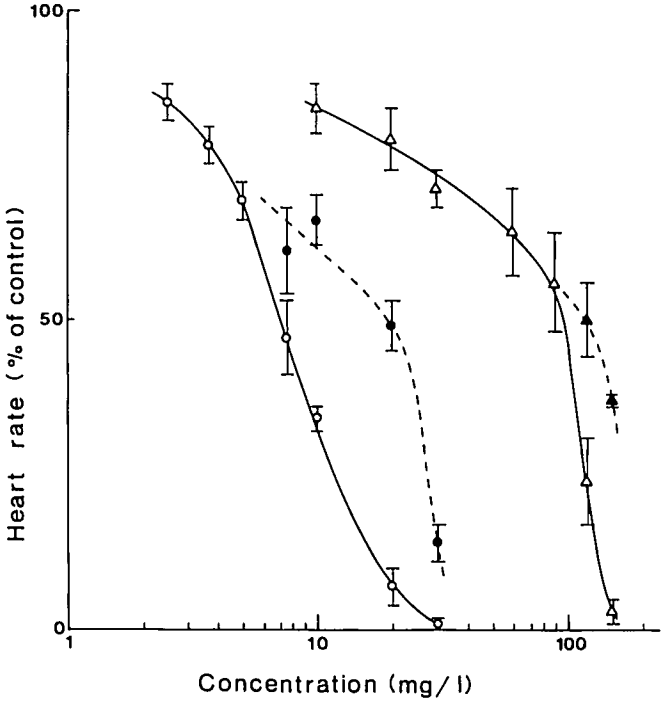

FIG. 1. Effect of bupivacaine and lidocaine on the heart rate. Media contained normal concentration of K^+ (5.9 mEq/l). (— O —) = bupivacaine, ventricular rate; (— Δ —) = lidocaine, ventricular rate; (– – ● – –) = bupivacaine, atrial rate when different from ventricular; (– – ▲ – –) = lidocaine, atrial rate when different from ventricular.

centrations studied were 5.9 mEq/l (normokalemia) and 8.0 and 9.0 mEq/l (hyperkalemia).

About 2 min elapsed before heart rate and aortic pressure reached new steady levels after the perfusate was changed. ECG and aortic pressure records were made 3–5 min after the beginning of the perfusion with a new medium. The perfusate was then changed back to the basal medium, and ECG and aortic pressure were recorded. This was followed by perfusion with a medium of different composition from that used in the previous experimental period. Thus, control periods (perfusion with the basal medium) and experimental periods (perfusion with a medium containing a local anesthetic and/or K^+ concentration of 8.0 or 9.0 mEq/l) were alternated. No particular sequence was followed in evaluating the effect of different media. Effects of an average of three different media were tested in this manner with each of 64 hearts. Deterioration of the preparation was minimum during the course of experiment (about one hour for each heart). Data were expressed either in terms of per cent of the value obtained during the preceding control period (*i.e.*, the period of perfusion with the basal medium) or in terms of absolute values in units of torr (mean aortic pressure), beats/min (heart rates), or seconds (PR interval). Each data point represents mean and standard error of mean of values obtained

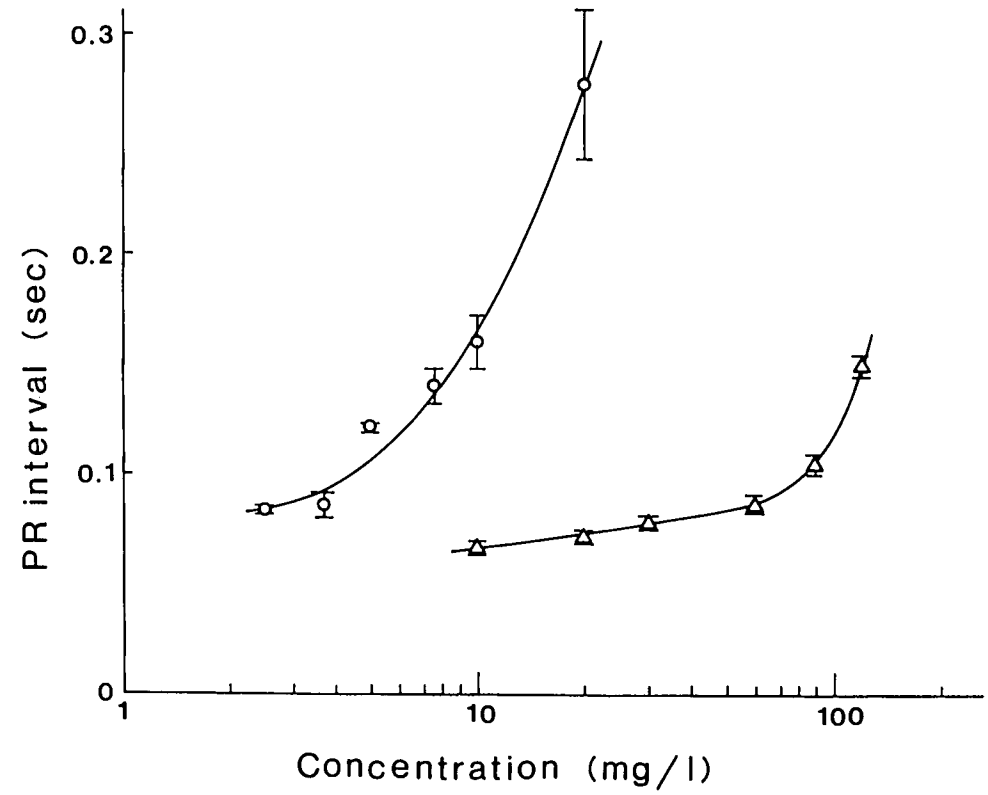

FIG. 2. Effect of local anesthetics on PR interval. Media contained a normal concentration of K^+ (5.9 mEq/l) (O) = bupivacaine, (Δ) = lidocaine.

TABLE 1. Effect of Bupivacaine and Lidocaine on Mean Aortic Pressure ([K+] = 5.9 mEq/l)

	Concentration (mg/l)	N	N (Asystole)	Mean aortic Pressure (Per Cent of Control)
Bupivacaine	2.5	5	0	100 ± 2
	3.75	6	0	100 ± 4
	5.0	9	0	97 ± 2
	7.5	7	0	104 ± 3
	10	5	0	97 ± 2
	20	6	1	86 ± 4*
	30	5	4	——†
Lidocaine	10	6	0	100 ± 1
	20	6	0	102 ± 2
	30	10	0	99 ± 2
	60	6	0	102 ± 2
	90	5	0	94 ± 2
	120	7	2	95 ± 2*
	150	5	3	——†

* Value for contracting hearts.
† No reliable value can be obtained because there were too few contracting hearts.

from 5 to 14 different hearts. Results were statistically evaluated by means of unpaired Student's *t* test.

Results

Cardiotoxic Effect of High Concentrations of Bupivacaine and Lidocaine

The isolated, perfused rat hearts had the following characteristics (mean ± SEM) during the control period, *i.e.*, during perfusion with the basal medium containing normal K^+ and no local anesthetics: mean aortic pressure, 83.7 ± 0.6 torr (n = 198); heart rate, 248 ± 2 beats/min (n = 198); and PR interval, 0.058 ± 0.001 s (n = 120, the smaller number as compared to the number for mean aortic pressure and heart rate is due to the fact that the P wave was obscured in some ECG traces). Bupivacaine and lidocaine had little effect on mean aortic pressure (table 1). Figure 1 shows the effect of bupivacaine and lidocaine on ventricular rate. Bupivacaine was 14-fold more effective

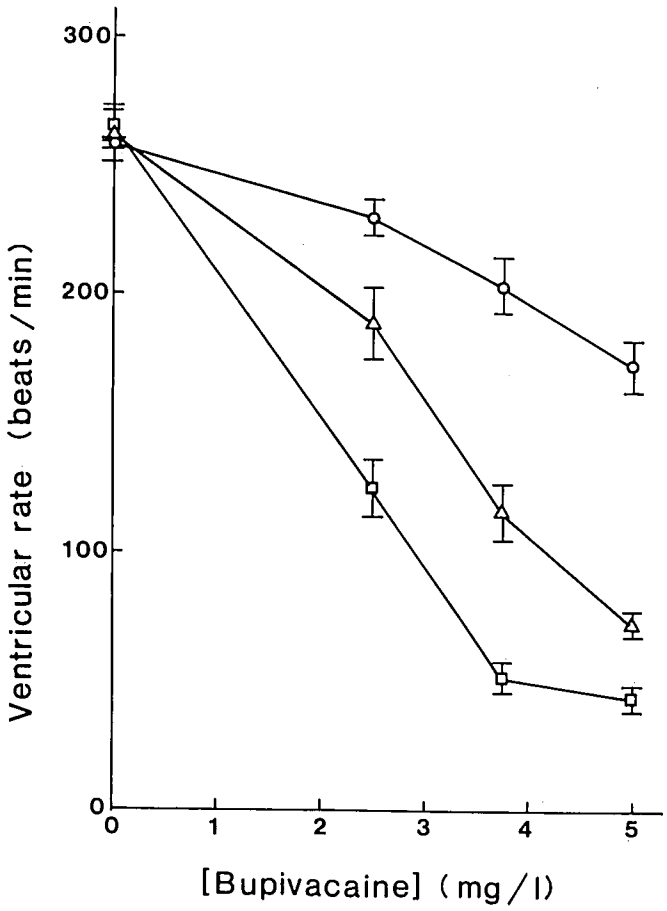

FIG. 3. Effect of hyperkalemia on bupivacaine inhibition of ventricular rate. K^+ concentrations: (○) = 5.9 mEq/l (normal); (△) = 8.0 mEq/l; (□) = 9.0 mEq/l.

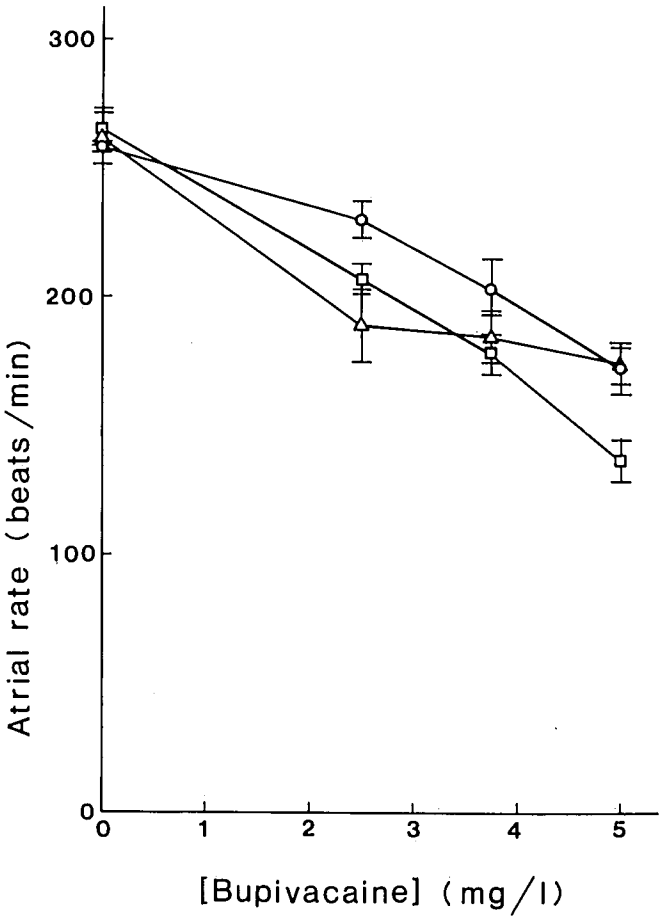

FIG. 4. Effect of hyperkalemia on bupivacaine inhibition of atrial rate. K^+ concentrations: (○) = 5.9 mEq/l (normal); (△) = 8.0 mEq/l; (□) = 9.0 mEq/l.

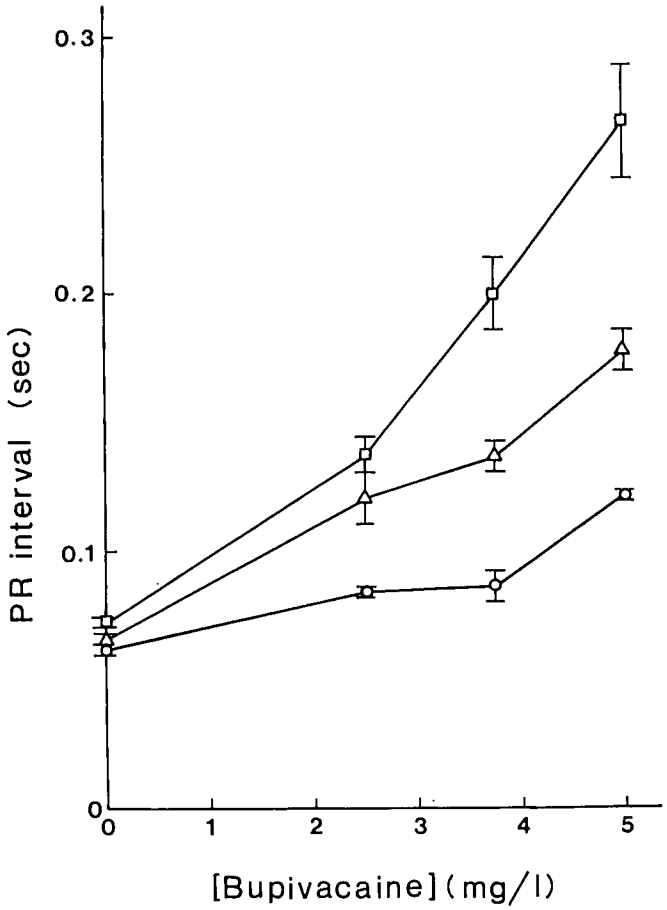

FIG. 5. Potentiation by hyperkalemia of bupivacaine effect on PR interval. K^+ concentrations: (O) = 5.9 mEq/l (normal); (Δ) = 8.0 mEq/l; (□) = 9.0 mEq/l.

than lidocaine in slowing the ventricular rate, as the concentration of bupivacaine for 50 per cent inhibition was 7 mg/l and that of lidocaine was 100 mg/l. On the other hand, bupivacaine was only 6-fold more effective than lidocaine in slowing atrial rate (the concentrations of bupivacaine and lidocaine for 50 per cent inhibition were 20 mg/l and 120 mg/l, respectively) (fig. 1). As can be seen in figure 2, bupivacaine was 17-fold more effective than lidocaine in increasing the PR interval, as the bupivacaine concentration for doubling PR interval was 6 mg/l while the corresponding value for lidocaine was 100 mg/l.

Potentiation by Hyperkalemia of the Cardiotoxicity of Relatively Low Concentrations of Bupivacaine

As can be seen in figure 3, the inhibitory effect of bupivacaine on ventricular rate was strongly enhanced by hyperkalemia. At each concentration of bupivacaine, the potentiation by hyperkalemia of 8.0 or 9.0 mEq/l was statistically significant ($P < 0.05$) as compared to the corresponding value obtained in the presence of the same concentration of the drug and a normal concentration (5.9 mEq/l) of K^+. Note that hyperkalemia (up to 9.0 mEq/l) had no effect on the ventricular rate in the absence of bupivacaine. Figure 4 shows that while bupivacaine slowed atrial rate, this effect was not appreciably potentiated by hyperkalemia when the concentration of bupivacaine was relatively low (up to 5.0 mg/l). This indicates that hyperkalemia, in the presence of relatively low concentrations of bupivacaine, acts to potentiate ventricular slowing by altering AV conduction rather than by affecting SA nodal pacemaker activity or conduction within the atria. Hyperkalemia in the absence of bupivacaine had little effect on PR interval (fig. 5). However, it potentiated the effect of bupivacaine on this variable. At each concentration of bupivacaine, the potentiation by hyperkalemia (8.0 or 9.0 mEq/l as compared to 5.9 mEq/l) was statistically significant ($P < 0.01$).

As would be expected from the well known effect of K^+ on the cardiotoxicity of lidocaine observed in other animal models,[2-4] hyperkalemia potentiated the effect of lidocaine in the perfused rat heart model used in this study. Figure 6 compares the effect of lido-

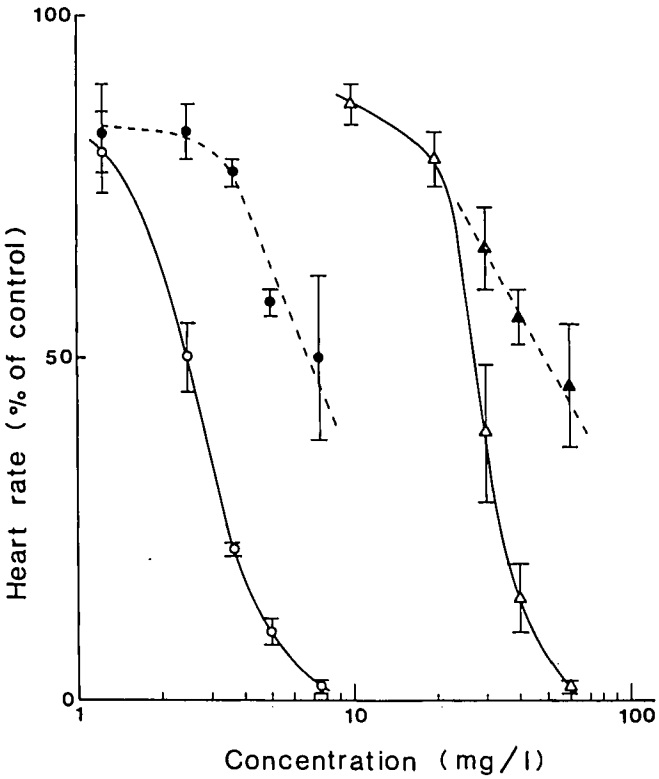

FIG. 6. Effect of local anesthetics on heart rate in the presence of 9.0 mEq/l of K^+. (— O —) = bupivacaine, ventricular rate; (— Δ —) = lidocaine, ventricular rate; (- - ● - -) = bupivacaine, atrial rate when different from ventricular; (- - ▲ - -) = lidocaine, atrial rate when different from ventricular.

caine to that of bupivacaine on heart rate in the presence of 9.0 mEq/l of K^+. The concentrations of bupivacaine and lidocaine for 50 per cent inhibition of ventricular rate were 2.5 mg/l and 28 mg/l, respectively, and the concentrations of bupivacaine and lidocaine for 50 per cent inhibition of atrial rate were 7 mg/l and 50 mg/l, respectively. Hyperkalemia potentiated the effect of lidocaine as well as that of bupivacaine in increasing the PR interval. Concentrations of bupivacaine and lidocaine for doubling the PR interval were 2 mg/l and 20 mg/l, respectively in the presence of 9.0 mEq/l or K^+ (data not shown). Both local anesthetics had little effect on mean aortic pressure in the presence of 9.0 mEq/l of K^+ (table 2) as in the presence of normal concentration of K^+ (See table 1).

TABLE 2. Effect of Bupivacaine and Lidocaine on Mean Aortic Pressure ($[K^+]$ = 9.0 mEq/l)

	Concentration (mg/l)	N	N (Asystole)	Mean aortic Pressure (Per Cent of Control)
Bupivacaine	1.25	10	0	103 ± 2
	2.5	6	0	95 ± 3
	3.75	5	0	91 ± 3
	5.0	7	0	91 ± 3
	7.5	6	4	——†
Lidocaine	10	8	0	95 ± 4
	20	5	0	93 ± 2
	30	8	2	94 ± 3*
	40	12	5	83 ± 5*
	60	7	5	——†

* Value for contracting hearts.
† No reliable value can be obtained because there were too few contracting hearts.

Discussion

The results of experiments reported in this paper indicate that bupivacaine, by virtue of a more potent effect on AV conduction, has higher cardiotoxicity than lidocaine in isolated, perfused working rat hearts. This conclusion is in agreement with the recent report by de Jong and Bonin[1] who showed that survival of mice undergoing seizure after bupivacaine injection was 15-fold lower than those undergoing seizure after lidocaine injection. We have shown in the present experiments that the cardiotoxic effects of the two local anesthetics were influenced differently by hyperkalemia. Hyperkalemia selectively potentiated AV block by relatively low concentrations (up to 5.0 mg/l) of bupivacaine. It caused little potentiation of the effect of bupivacaine on atrial rate. No such selectivity was noted with lidocaine. Figures 1 and 6 demonstrate that ventricular slowing by lidocaine is achieved by an appreciable effect on atrial rate as well as by an effect on the degree of AV block.

While the currently used local anesthetics have been found to be generally safe, reports of profound bradycardia and cardiac arrest,[8,9] although rare, make it extremely important to identify conditions which influence the cardiotoxic actions of these drugs. Arrival of the local anesthetic at the heart prior to extensive dilution, competitive binding, inhibition of sympathetic activity, and postseizure hypoxia and acidosis, are conditions which are known to influence cardiotoxicity.[10] Our experiments were carried out in isolated hearts perfused with media containing no protein, and all the media were equilibrated with a nonvarying gas mixture of 95 per cent O_2–5 per cent CO_2. Our model was therefore not influenced by changes in competitive binding or by postseizure hypoxia and acidosis. It should also be noted that our model was devoid of autonomic influence.

The results of our study show that mild hyperkalemia potentiates the cardiotoxicity of lidocaine and bupivacaine. One cannot automatically assume that these results, derived from the isolated rat hearts, are directly applicable to the clinical situation. However, the well-known effect of variation of extracellular K^+ concentration on the cardiac actions of lidocaine in other animal models[2–4] suggests that the potentiating action of hyperkalemia which we observed is not unique to the rat.

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