

## The Electrophysiologic Actions of Lidocaine and Bupivacaine in the Isolated, Perfused Canine Heart

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To discriminate between the electrophysiologic and arrhythmogenic effects of lidocaine and those of bupivacaine, isolated, perfused canine hearts were exposed to toxic concentrations of the drugs. The preparations included the sinus node and right atrium, and, in some cases, the AV node and interventricular septum as well. Action potentials were recorded from these areas, and right atrial twitch amplitude and spontaneous rate and rhythm were monitored. Heart rate was depressed in a dose-dependent manner by both drugs, as was atrial twitch amplitude. In the absence of arrhythmias, the spontaneous rate decreased less than 30% with lidocaine up to 50 µg/ml, and with bupivacaine up to 5 µg/ml. The twitch depression reflected a potency ratio for bupivacaine (mol. wt. 288) to lidocaine (mol. wt. 234) on a mass basis of 8.1:1. The most prominent arrhythmia found was sinoatrial block, which was caused by both drugs with a potency ratio for bupivacaine to lidocaine of 15.4:1 and was reversed by 0.02 µg/ml norepinephrine. Sinus arrhythmias, block of retrograde conduction from AV node to atrium, and irregular rhythms originating within the AV node were observed with both drugs at concentrations similar to those which produced sinoatrial block. The atrial action potential revealed decreased upstroke velocity, overshoot, and height with both lidocaine and bupivacaine, with potency ratios (bupivacaine:lidocaine) ranging from 15:1 to 26:1. In septal cells, both drugs depressed upstroke velocity, and bupivacaine lengthened action potentials by up to 14%, but lidocaine did not. The major difference between bupivacaine and lidocaine in this study was the higher potency of the former agent with respect to electrophysiologic end-points. (Key words: Anesthetics, local; bupivacaine; lidocaine. Heart: action potentials; arrhythmias; atrioventricular node; sino-atrial block; sino-atrial node.)

THE POTENTIAL FOR major cardiovascular toxicity following injection of the highly lipid soluble local anes-

thetics, etidocaine and bupivacaine, has been widely recognized since the report of six cases by Albright.<sup>1</sup> Cardiac arrhythmias of various types (including asystole,<sup>1</sup> nodal bradycardia,<sup>2</sup> complete heart block,<sup>1</sup> and ventricular tachycardia and fibrillation<sup>3,4</sup>) have been described. Results from intact animal models in which ventilation is not supported suggest that bupivacaine may produce earlier circulatory collapse (relative to CNS toxicity) and more significant EKG changes than lidocaine.<sup>5,6</sup> When ventilation is supported during drug infusion in similar animal studies, supraventricular and ventricular arrhythmias and electromechanical dissociation have been variously observed,<sup>7-11</sup> and bupivacaine was found to be more toxic than lidocaine in some of these models. Together, these studies suggest that cardiac conduction and rhythm disturbances are associated with bupivacaine,<sup>12</sup> but, with the exception of widened QRS complexes, no EKG finding or arrhythmia occurred consistently with bupivacaine.

Studies in isolated heart tissue have demonstrated that, in protein-free solution, bupivacaine (mol. wt. 288) is highly potent relative to lidocaine (mol. wt. 234) with respect to negative chronotropic, dromotropic, and inotropic effects. Potency ratios (bupivacaine:lidocaine) range from 9:1 to 50:1 on a mass basis.<sup>13-15</sup> § These ratios are markedly greater than the widely accepted potency ratio of 4:1 for neural blockade.<sup>16</sup> Also, in isolated, perfused guinea pig hearts, AV block and premature ventricular contractions were noted with bupivacaine, but not with lidocaine.<sup>17</sup>

Since some experiments have indicated that bupivacaine may be arrhythmogenic, but have not defined a mechanism, we have addressed the question of bupivacaine's cardiotoxicity (or arrhythmogenicity) in a cardiac preparation that allows us to probe its entire conduction system and is independent of neural and humoral inputs. The isolated, perfused canine right atrium provides 1) a conduction system with functional and anatomic similarity to the human, 2) anatomic integrity of that system from the sinus node to the interventricular septum, and 3) access to sinus node, right atrium, AV node, and septal cells for microelectrode studies.

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§ Block A, Covino BG: Effect of local anesthetic agents on cardiac conduction and contractility. Reg Anesth 6:55-61, 1981

## Methods

### EXPERIMENTAL PREPARATIONS

Mongrel dogs (<6 months), weighing 3–7 kg, were heparinized and then anesthetized with sodium pentobarbital (30 mg/kg), and the heart was rapidly excised through a right thoracotomy. The heart was rinsed in chilled Ringer's solution, and coronary arteries were cannulated and perfused according to one of the following two procedures, both of which have been previously described in detail.<sup>18,19</sup>

To obtain a preparation which includes a viable right atrium and sinus node, the proximal right coronary artery was cannulated with a 19-G catheter. Ventricular branches and the right coronary distal to the sinus node artery were ligated. Perfusion of Krebs-Ringer solution (for composition, see below) was provided by a constant infusion pump at a rate of 4 ml/min.

For preparations which included not only the right atrium and sinus node, but also the AV node and portions of the interventricular septum, three coronary arteries were cannulated. Catheters (19G) were inserted into the septal branch of the left anterior descending at its origin, the proximal left circumflex to perfuse its AV node branch, and the proximal right coronary. Distal branches supplying unwanted regions were ligated. Perfusion of Krebs-Ringer solution was maintained to the three cannulae at a total flow of 10 ml/min. The right and left ventricular free walls were removed, and a cut was made in the right atrial free wall along the margin of the right atrial appendage from the AV sulcus to the superior vena cava. The lateral portion of the right atrial appendage was then retracted to expose the right atrial endocardial surface.

For both preparation types, the heart was pinned to the floor of a tissue bath, and the venous effluent filled the bath so as to continuously bathe the preparation. The overflow was discarded. Upon establishment of perfusion, all preparations regained and maintained (in the absence of drugs) a regular rhythm. In the preparations with three cannulae, AV conduction was also regained.

The perfusion solution contained (in mM): Na 145, K 4.2, Ca 1.3, Mg 0.85, Cl 124, HCO<sub>3</sub> 25, SO<sub>4</sub> 0.85, H<sub>2</sub>PO<sub>4</sub> 2.4, and dextrose 5.6. Solutions were bubbled with 5% CO<sub>2</sub>/95% O<sub>2</sub> to maintain a pH of 7.4, and warmed so that the temperature recorded on the endocardial surface of the right atrium was 36.5 ± 0.7° C. A four-way diverting valve just proximal to the vascular cannulae provided the ability to rapidly switch between control (drug-free) solution and perfusate of identical composition containing the local anesthetics lidocaine (Astra) or bupivacaine (Winthrop-Breon).

### PREPARATION MONITORING

A strain gauge was coupled to the right atrium with a silk suture. Resting tension was so oriented that maximal atrial shortening was achieved. Strain gauge signals were recorded on a chart recorder (Hewlett-Packard 7754A).

In most preparations, a silver bipolar electrode was sutured to the tissue, and surface electrograms were recorded on the chart recorder to monitor rate and rhythm. External stimulation could be provided by a movable silver bipolar electrode carrying rectangular constant current pulses through a stimulus isolation circuit (Grass). Threshold current was determined empirically with pulses 5 msec in duration; current was then reset to approximately 50% above threshold. Threshold current (or pulse duration up to 10 msec) was re-determined and reset when pulses failed to elicit action potentials.

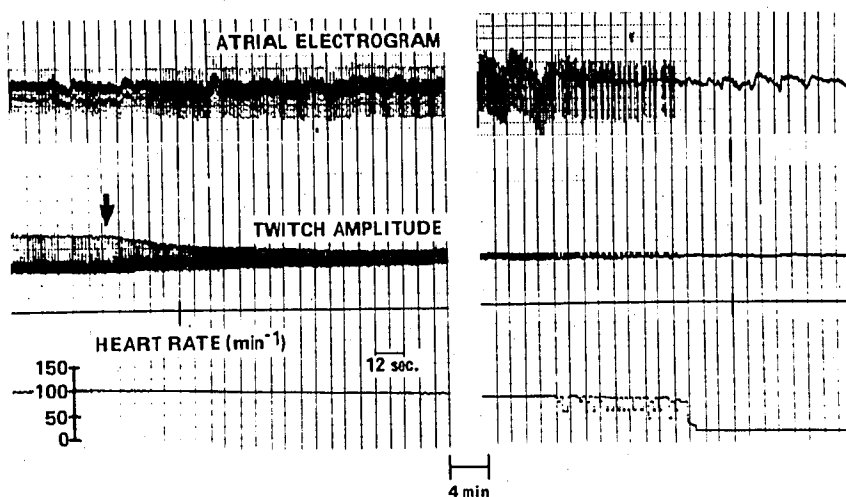
### MICROELECTRODE RECORDINGS

Conventional microelectrode techniques were used to record transmembrane potentials. Glass capillaries were drawn to a tip having resistance of 10–40 MΩ after filling with 3M KCl. The electrode tips were then honed and bevelled in an alumina slurry<sup>20</sup> to a final tip resistance of 5–20 MΩ. For impalements, the electrodes were suspended on a spiral silver wire which provided sufficient rigidity to penetrate the endocardium or epicardium with enough flexibility to accommodate tissue movement. A Gould digital storage oscilloscope (4040) displayed the outputs from a WPI microelectrode amplifier (KS-700). Analog differentiation of the voltage signal was provided by a WPI d/dt differentiator. Data was stored by photography of the oscilloscope screen.

### EXPERIMENTAL PROTOCOLS

Preparations which included the right atrium and sinus node (single cannula) were utilized for action potential recordings, measurements of spontaneous heart rate, and determination of right atrial twitch amplitude. Electrophysiologic recordings of the AV node and septum were performed in those hearts in which three vessels were cannulated. Spontaneous heart rate and right atrial twitch amplitude was also monitored in these preparations. Each experiment began with a 30-min stabilization period of control perfusion, followed by further perfusion with control solution for at least 30 min, during which baseline recordings were obtained. Solution containing a constant concentration of either lidocaine or bupivacaine was then perfused for a 60–180-min interval. It was not possible to maintain microelectrode impalements for a sufficient length of time to reliably capture electrophysiologic phenomena

FIG. 1. Spontaneously beating perfused right atrial preparation acutely perfused with lidocaine 40  $\mu\text{g}/\text{ml}$  (at arrow). Atrial electro-mechanical quiescence occurs approximately 7.5 min after exposure to lidocaine and after a brief period of arrhythmia. The electrogram was recorded from a bipolar electrode on the epicardial surface. Twitch amplitude represents deflections from right atrial contraction.



at the solution change. Impalement attempts were restarted 3 min into perfusion with lidocaine and 5 min into perfusion with bupivacaine. The vast majority of impalements were obtained between 10 and 90 min after the start of local anesthetic exposure. Drug wash-out was accomplished by a 30-min control perfusion, after which control recordings were again made. In some hearts, a second local anesthetic perfusion was done, using a constant concentration typically of the opposite drug (lidocaine or bupivacaine) and beginning after not less than 60 min of perfusion with drug-free solution. The order in which the drugs were applied was varied. The second drug application was again followed by a washout and control recording period. Hearts were not used for more than two drug perfusion cycles.

#### STATISTICAL ANALYSIS

Sinus node rates before and after atrial quiescence were compared by paired *t* test. Potency ratios for twitch depression and action potential parameters were developed by performing linear regressions to determine the relationship between each endpoint and the logarithm of drug concentration. Where the slopes significantly differed from zero ( $F > \text{critical value}$ ), the dose-response curve slopes for the two drugs were compared by *t* test. If no significant difference in slopes was found, a potency ratio was computed by forcing the two regression lines to have the same slope. The potency ratio based on the frequency of atrial quiescence was computed by probit analysis. The difference in the rate of development of twitch depression between lidocaine and bupivacaine was measured by computing a 95% confidence interval on the logarithm of the ratio of the time constants for the two groups. Pearson's correlation coefficients were used to measure the association between these time constants and drug dose or heart rate.

Co-variance analysis was used to adjust the measured action potential parameters for the effect of heart rate. The significance of differences of action potential parameters from control was determined by analysis of variance and Fisher's protected least significant difference test. For comparisons of action potential parameters within an individual experiment (drug *vs.* control), analysis of variance and Fisher's protected least significant difference test were also used.

#### Results

##### MECHANICAL ACTIVITY

All preparations exhibited a reduction in the twitch amplitude of the right atrium immediately upon perfusion with local anesthetic (fig. 1). This effect was reversible on return to a drug-free perfusate. The onset of twitch depression was dominated by a single exponential component for the first 2 min after exposure to lidocaine and for the first 3 min after exposure to bupivacaine. The median time constant of this major component of twitch depression was 61 s (range 32–182;  $n = 29$ ) for lidocaine and 113 s (range 58–222;  $n = 22$ ) for bupivacaine, a statistically significant difference ( $P < 0.001$  both by parametric and nonparametric tests). Correlations between these time constants and either heart rate or drug dose were not statistically significant ( $P > 0.14$ ).

In addition to the major and readily quantifiable component discussed above, slow changes in the twitch amplitude, of variable direction and small magnitude, were seen in most hearts. The rate of change of twitch depression, therefore, dictated the analysis of the magnitude of the response. With the goal being to incorporate the majority of the depression seen in each preparation while minimizing the influence of the variable slow responses, a point approximately three time constants

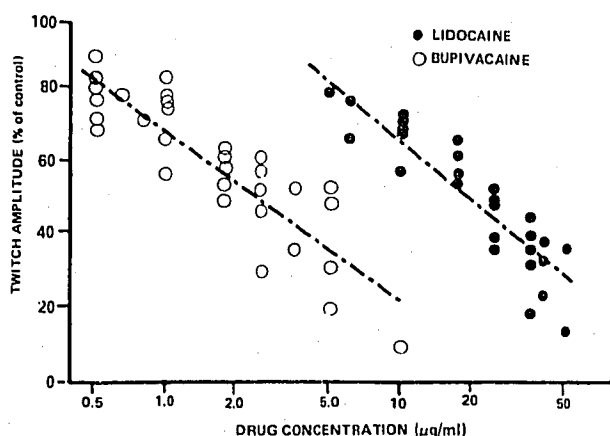


FIG. 2. Dose-response curves for depression of right atrial twitch amplitude by lidocaine (●) and bupivacaine (○). The dashed lines were derived by linear regression.

after the switch to drug-containing solution was analyzed. Thus, the twitch amplitude 3 min after exposure to lidocaine and 5 min after exposure to bupivacaine was chosen as the endpoint for analysis of the amount of twitch depression. The control twitch amplitude was the value immediately prior to each drug exposure, and all results are expressed as percent of control.

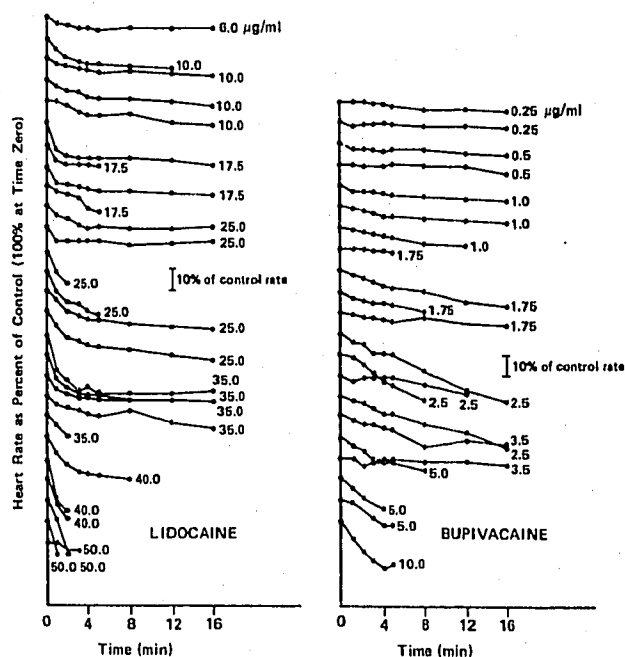


FIG. 3. A family of curves representing heart rate changes over time during perfusion of spontaneously beating preparations with lidocaine or bupivacaine. Each curve represents an individual preparation. The drug dose in  $\mu\text{g/ml}$  is shown at the end of each curve. Heart rates are plotted as percent of control with the time 0 point representing 100% of control for that preparation.

TABLE 1. Atrial Quiescence Within 60 Min of Drug Exposure

Bupivacaine			Lidocaine		
Dose ( $\mu\text{g/ml}$ )	Total Number of Hearts	Number Quiescent	Dose ( $\mu\text{g/ml}$ )	Total Number of Hearts	Number Quiescent
0.5	3	0	5	1	0
0.8	1	0	10	2	0
1.0	3	0	17.5	5	1
1.75	5	2	25	6	2
2.5	6	5	35	5	1
3.5	2	1	40	3	3
5.0	5	5	50	3	3
7.5	1	1	100	1	1
10.0	1	1			

The dose-response curves for twitch depression are shown in figure 2. The slopes of the curves for lidocaine and bupivacaine are not significantly different ( $P = 0.31$ ). The relative potency of the two drugs for this end-point is 8.1:1 (bupivacaine:lidocaine) on a mass basis. Other approaches to end-point definition (such as utilizing the time constant for an individual preparation to define the point three time constants after drug exposure) did not alter this figure (*i.e.*, each result lay within the 95% confidence limits of the others).

#### SPONTANEOUS RATE

Both lidocaine and bupivacaine depressed the spontaneous rate of isolated right atrial preparations. A composite of the response is shown in figure 3, which includes only rates prior to the onset of arrhythmias. At the higher doses of both drugs, arrhythmias often did intervene. In those preparations which maintained a regular atrial rate, it was rare for a greater than 30% rate decrement to be observed. The response to lidocaine appeared to be more rapid than that to bupivacaine. However, the experimental variability was such that a clear picture of the rate response could not be defined.

#### RHYTHM DISTURBANCES—SINO-ATRIAL BLOCK

In many preparations perfused with local anesthetic-containing solution, a cessation of right atrial electrical and mechanical activity was observed (fig. 1). This occurred at variable times (range: 30 s to 91 min) after the beginning of drug perfusion. The onset of atrial electromechanical quiescence was more rapid with lidocaine than with bupivacaine, and tended to be more rapid with higher concentrations of either drug. The quiescence is also clearly dose-dependent, as shown in table 1. By probit analysis, a relative potency of 15.4 (95% confidence limits: 10.0–25.7) for bupivacaine to lidocaine on a mass basis was found. In all cases of atrial quiescence, spontaneous electrical and mechanical ac-

tivity resumed after drug washout. Norepinephrine, in concentrations of 0.02 µg/ml or greater, was infused with the local anesthetic in four quiescent atria, and restored activity in each.

In those quiescent atria in which successful microelectrode impalements were made in the sinus node region (15 instances of quiescence in 13 different hearts), APs typical of that area could be recorded (fig. 4). The sinus node rate at the first recording after atrial quiescence was similar to the last regular rate prior to quiescence ( $P > 0.5$  by paired *t* test). By qualitative observation, the APs in and around the sinus node of quiescent atria formed a continuum from those nearly identical to normal sinus node APs, then to electrotonic potentials of small amplitude, and finally to atrial muscle cells with no electrical activity, only a stable resting potential. The changes in transitional cells (cells near the sinus node which exhibit phase 4 depolarization, but which do not have a smooth transition from phase 4 to phase 0) could be quantified on the basis of seven atria in which recordings in such regions were made (table 2). As shown in figure 5, the abrupt transition between phases 4 and 0 was lost and the maximum rate of depolarization tended to decrease (statistically significant only with bupivacaine).

In the sinus node and transitional region, several additional phenomena related to arrhythmias were observed. During local anesthetic perfusion in several hearts, cells were impaled which exhibited alternating AP configurations. Examples are shown in figure 6, and may relate to a halving of atrial rate seen in some preparations. That is, the more attenuated (lower overshoot and maximum rate of depolarization) AP of the pair may represent a slowly conducted impulse which does not result in excitation of the bulk of atrial working muscle. In two atria which retained a regular rate and rhythm during local anesthetic perfusion, action potentials at multiple sites along the crista terminalis near the sinus node were sequentially recorded. These records, shown in figure 7, illustrate a variety of abnormal com-

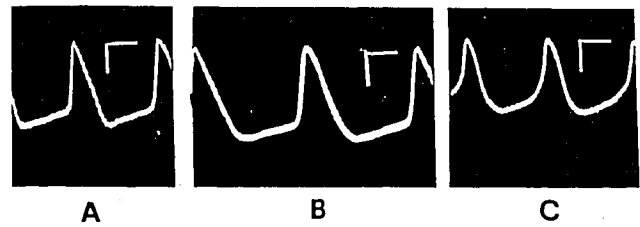


FIG. 4. Action potentials recorded from sinus node region of perfused right atria. A. Control solution—atrium beating. B. Lidocaine 35 µg/ml—atrium quiescent. C. Bupivacaine 5 µg/ml—atrium quiescent. Calibration bars: horizontal 200 msec; vertical 20 mV. Position of horizontal calibration bar represents 0 mV.

pound AP configurations even in these hearts without gross arrhythmias.

#### ACTION POTENTIAL CONFIGURATION— RIGHT ATRIUM

Lidocaine and bupivacaine altered the APs of right atrial muscle cells in a similar fashion. When data from all experiments are considered together, statistically significant differences between drug-treated and control were seen in the overshoot potential, AP height, and maximum rate of depolarization (table 3). There is a variable response of the AP duration to both drugs, with a significant increase in duration seen only with two concentrations of bupivacaine. The resting potential was not altered. The reductions in overshoot, AP height, and maximum rate of rise are clearly dose-dependent for both drugs. The potency ratios (bupivacaine:lidocaine on a mass basis) are 20:1 for maximum rate of rise, 15:1 for overshoot, and 26:1 for AP height.

In those hearts where a sufficient number of action potentials were recorded in both the drug-treated and control conditions to justify statistical analysis, the reductions of the overshoot, action potential height, and maximum rate of rise were again observed (table 4). Increases in AP duration, beyond that expected because of decreases in heart rate, were present only in a few preparations.

TABLE 2. Transitional Cell Action Potential Characteristics

Solution	N <sub>h</sub>	N <sub>i</sub>	Rate (min <sup>-1</sup> )	MDP (mV)	Takeoff Potential (mV)	Overshoot (mV)	MRD (V/sec)	APD <sub>50</sub> (msec)	Phase 4 Depolarization	
									Early (V/sec)	Late (V/sec)
Control	7	22	86 ± 15	-62 ± 7	-54 ± 5	4.4 ± 4.2	11.5 ± 11.0	129 ± 13	.045 ± .026	.0056 ± .0049
Lidocaine (25-35 µg/ml)	3	7	67 ± 2*	-61 ± 6	-53 ± 6	2.0 ± 5.2	4.1 ± 2.9	143 ± 17*	.026 ± .008	.0058 ± .0014
Bupivacaine (1.75-2.5 µg/ml)	3	5	86 ± 14 <i>P</i> < .05	-60 ± 3 NS	-54 ± 2 NS	1.2 ± 8.0 NS	2.0 ± 1.2* <i>P</i> = .05	143 ± 7* <i>P</i> < .05	.036 ± .013 NS	.0084 ± .0078 NS

Figures stated as mean ± standard deviation. N<sub>h</sub> = number of hearts; N<sub>i</sub> = number of impalements (one AP per impalement); MDP = maximum diastolic potential; MRD = maximum rate of depolarization; APD<sub>50</sub> = action potential duration at 50% repolarization; NS

= not significant.

Significance indicates differences between groups in the columns; \*denotes a significant difference from control.

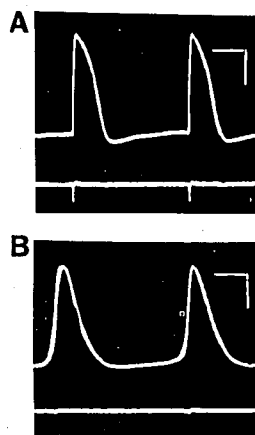


FIG. 5. Action potentials from the same point in the transitional region near the sinus node of one preparation. The lower oscilloscope trace in each panel is the first time derivative of voltage (downward deflection indicates positive  $dV/dt$ ). A. Control solution. B. Bupivacaine 5  $\mu\text{g/ml}$ . Calibration bars: horizontal = 200 msec; vertical = 20 mV for action potentials, 40 V/sec for  $dV/dt$ . Position of horizontal bar marks 0 mV.

#### ACTION POTENTIAL CONFIGURATION—INTERVENTRICULAR SEPTUM

In most preparations under control conditions, the septal AP consisted of a prominent initial spike followed by a rounded plateau. Both lidocaine and bupivacaine caused a reduction of this initial spike amplitude at lower concentrations and eliminated it at higher concentrations (fig. 8). The height of the plateau and the resting potential showed no significant change with either drug (table 5). The maximum rate of rise was depressed by both drugs. However, with lidocaine, no clear dose-dependent relationship was found over the concentration range studied (10–50  $\mu\text{g/ml}$ ). This may represent experimental variability and the relatively narrow dose range, since the expected dose relationship was found with bupivacaine. The AP duration lengthened with bupivacaine, although not in a dose-dependent manner. With lidocaine, no significant trends were seen in the AP duration; however, slight shortening occurred at the higher concentrations. Comparisons of



FIG. 6. Action potentials recorded near the sinus node demonstrating alternating configurations. A. Bupivacaine 5  $\mu\text{g/ml}$ ; remainder of atrium is quiescent. B. Bupivacaine 1.75  $\mu\text{g/ml}$ ; action potentials occurring in alternation but here fortuitously overlapping on consecutive oscilloscope sweeps; the atrium beat at a rate equal to  $1/2$  of the rate of these action potentials. For both panels: horizontal calibration bar marks 0 mV and length = 200 msec; vertical calibration bar = 20 mV.

control and drug-treated conditions within individual preparations yielded identical conclusions (table 6).

#### RHYTHM DISTURBANCES—AV NODE

Examination of gross rhythms and of action potentials in the AV node region revealed that both lidocaine and bupivacaine induced a variety of rhythm disturbances in those preparations in which the right atrium, AV node, and interventricular septum were perfused. Right atrial quiescence was seen in these preparations with higher concentrations of either drug. Spontaneous nodal and septal activity were typically present after atrial quiescence, but at a rate much lower than that preceding quiescence. The septal tissue could be driven by an extracellular stimulating electrode after atrial quiescence, and action potentials in the AV node following septal stimuli could also be recorded. However, no atrial activity could be recorded with septal stimulation in those preparations exhibiting atrial standstill. On one occasion, the right atrium followed a stimulus applied directly to its endocardial surface after quiescence, indicating that the cessation of activity was not due to complete atrial inexcitability, but rather to conduction blockades at the sinus node region and the AV node region. (It is of interest that, in this preparation, the AV block was unidirectional; that is, spontaneous activity in the AV node and septum was not transmitted to the atrium, but the stimulated atrial beats produced a one-for-one response in the septum.) Irregular rhythms involving the AV node and septum were relatively common in these preparations with both local anesthetics. In 17 preparations which included atrium, AV node and septum and were exposed to lidocaine or bupivacaine, nine developed an arrhythmia other than atrial quiescence. Examples of these rhythms include second degree block between AV node and septum, premature septal beats, and variable activation patterns within the AV node (figs. 9, 10).

#### Discussion

##### EFFECTS ON HEART RATE

In the isolated dog right atrium, dose-dependent decreases in spontaneous heart rate occurred with both lidocaine and bupivacaine. However, at concentrations of lidocaine up to 50  $\mu\text{g/ml}$  and bupivacaine up to 5  $\mu\text{g/ml}$ , these changes were relatively small, with no more than a 30% decrease seen as long as regular rhythm was maintained. Even in those preparations in which right atrial activity ceased (because of sino-atrial block), the sinus node continued to fire at a rate similar to that observed before right atrial quiescence. Thus, at these drug concentrations, the rate of the pacemaker

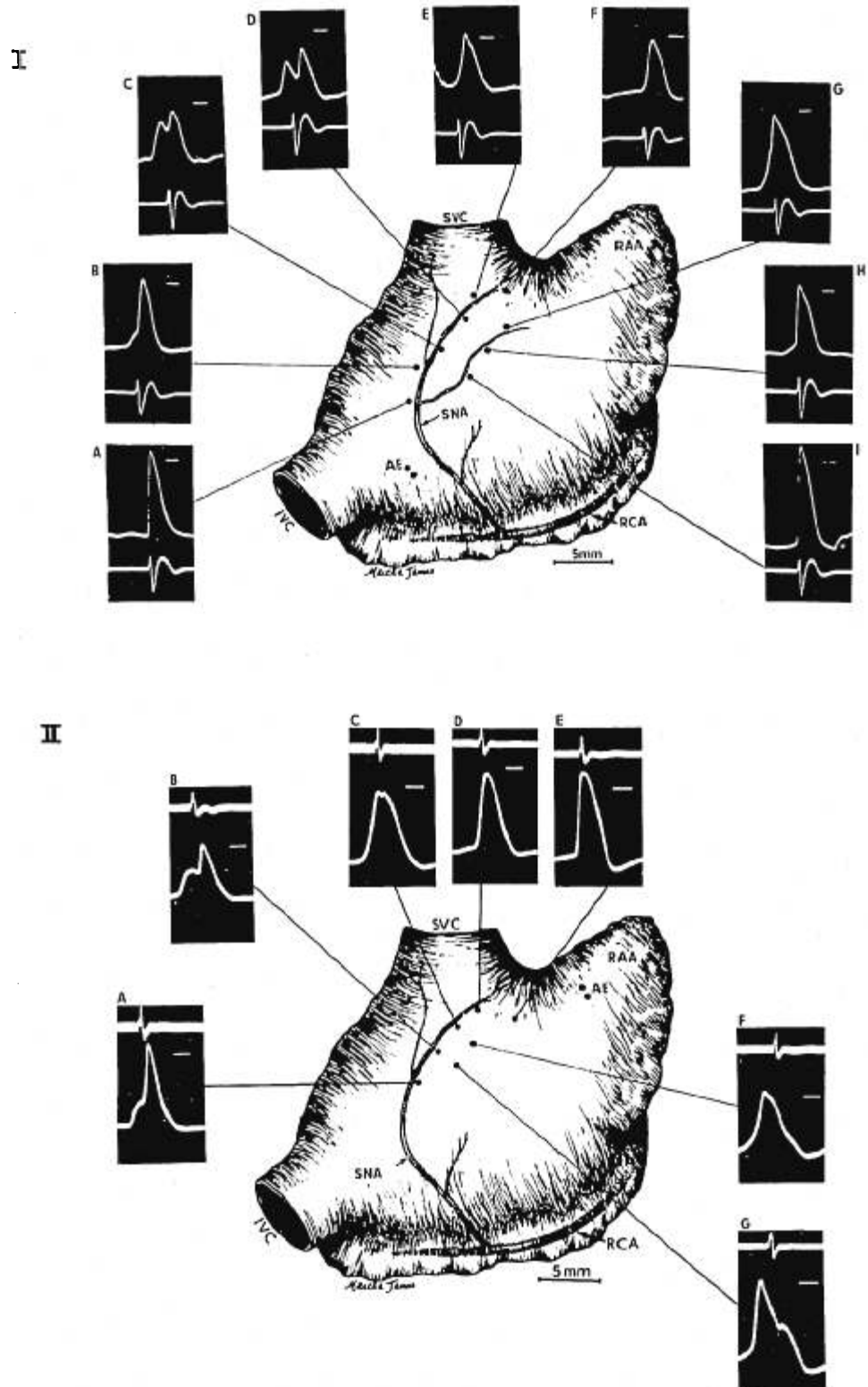


FIG. 7. Action potentials recorded near sinus node in two spontaneously beating, perfused right atria. *I.* Lidocaine 25 µg/ml. The lower traces in these panels represent the atrial bipolar electrogram (AE). *II.* Bupivacaine 2.5 µg/ml. The upper traces in these panels are the AE. For both panels: SVC = superior vena cava; RCA = right coronary artery; SNA = sinus node artery; RAA = right atrial appendage. The horizontal bar in each panel marks 0 mV. Horizontal calibration bar = 200 msec. Vertical calibration bar = 20 mV for action potentials.

was decreased, but other actions appeared to be more important with respect to overall changes in cardiac function. Other investigators report similar findings of

minor depression of sinus node rates for comparable dose ranges of lidocaine and bupivacaine.<sup>13,21</sup> These reports also show that the pacemaker rate declines further

TABLE 3. Action Potential Characteristics in Atrial Working Muscle (Rate Corrected)

Concentration ( $\mu\text{g/ml}$ )	$N_h$	$N_i$	Rate ( $\text{min}^{-1}$ )	Resting Potential (mV)	Overshoot (mV)	AP Height (mV)	APD <sub>50</sub> (msec)	dV/dt <sub>max</sub> (V/sec)
<b>Bupivacaine</b>								
0 (Control)	13	90	88.4	-76.0	22.7	98.2	110	221
0.5	3	10	95.5	-74.6	19.9	94.6	112	102*
1.0	3	11	100.5	-74.6	14.6*	89.1*	112	96*
1.75	2	10	88.7	-77.8	8.2*	86.0*	113	69*
2.5	2	14	93.8	-77.3	15.2*	92.0*	129*	77*
3.5	1	6	84.5	-74.9	10.6*	85.6*	130*	60*
5.0	2	2	118	-73.6	10.4*	83.8*	92	24*
Standard deviation				4.4	4.8	6.1	17	59
Significance				.74	.0001	.0001	.0041	.0001
<b>Lidocaine</b>								
0 (Control)	10	60	87.4	-76.7	22.7	99.3	115	213
5	1	7	100.3	-73.6	23.5	96.6	95	221
10	2	11	82.1	-73.5	16.6*	90.1*	109	101*
17.5	1	11	121.4	-78.6	16.4*	94.6*	126	93*
25	3	18	76.9	-77.9	13.9*	92.4*	130	104*
35	3	12	89.4	-78.4	10.3*	88.6*	124	56*
40	1	1	86.0	-78.0	6.8*	84.8*	126	77*
Standard deviation				4.4	4.5	6.0	17	56
Significance				.91	.0001	.0001	.081	.0001

$N_h$  = number of hearts;  $N_i$  = number of APs (one AP per impalement); AP = action potential; APD<sub>50</sub> = action potential duration at 50% depolarization; dV/dt<sub>max</sub> = maximum rate of depolarization (phase 0). The significance figures represent *P* values for comparison of the control group and any drug level in a column. The AP charac-

teristics are corrected for effect of heart rate using covariance analysis. The standard deviations were computed from the error term of the covariance analysis.

\* Significantly different from control.

at doses higher than those used here and that a potency ratio in the range of 6:1–8:1 (bupivacaine:lidocaine) pertains to this endpoint.

#### DEPRESSION OF CONTRACTILITY

In all studies of isolated tissue exposed to lidocaine and bupivacaine, indices of contractility decline in a

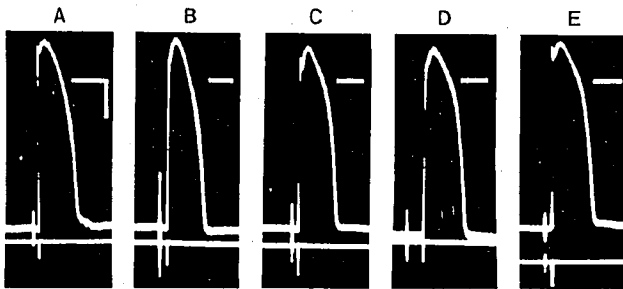


FIG. 8. Action potentials recorded from the interventricular septum of one preparation sequentially perfused with control solution (A), lidocaine 35  $\mu\text{g/ml}$  (B), control solution (C), bupivacaine 1.75  $\mu\text{g/ml}$  (D), and control solution (E). The lower trace in each panel represents the first time derivative of voltage with downward deflections reflecting positive dV/dt. Heart rate is 87  $\text{min}^{-1}$  in each panel. The horizontal calibration bar (shown in panel A) represents 200 msec; the position of the horizontal bar in each panel marks 0 mV. The vertical calibration bar represents 20 mV for the upper traces, 400 V/sec for the lower trace in panel A, and 200 V/sec for the lower traces of panels B–E.

dose-dependent manner. Block and Covino,<sup>11</sup> in isolated rabbit hearts, saw a 25% reduction in dp/dt<sub>max</sub> at 1.4  $\mu\text{g/ml}$  bupivacaine and 16.4  $\mu\text{g/ml}$  lidocaine, a potency ratio of approximately 12. Bupivacaine 5  $\mu\text{g/ml}$  was found to be slightly more potent than lidocaine 50  $\mu\text{g/ml}$  in decreasing the contractile force of isolated guinea pig atria.<sup>15</sup> In guinea pig papillary muscles, depression of tension generation by bupivacaine 1.2  $\mu\text{g/ml}$  was very similar to that by lidocaine 9.4  $\mu\text{g/ml}$ .<sup>22</sup> Our results show parallel dose-response curves for depression of right atrial twitch amplitude by the two drugs, with a potency ratio of 8.1:1, similar to the above-cited studies.

The cardiac depressant actions of bupivacaine take almost twice as long to develop as those of lidocaine, in parallel to the time course of neural blockade. The clinical corollary in terms of local anesthetic toxicity is that, because of bupivacaine's greater latency in producing toxic endpoints, relatively more of the drug will be required for the adverse cardiovascular actions to become apparent during intravascular injection.

#### SINO-ATRIAL BLOCK

In our isolated dog right atrial preparations, the most prominent arrhythmia with both lidocaine and bupiva-

<sup>11</sup> Block A, Covino BG: Effect of local anesthetic agents on cardiac conduction and contractility. *Reg Anesth* 6:55–61, 1981



TABLE 4. Action Potential Characteristics in Atrial Working Muscle: Comparisons to Controls within Individual Preparations

Concentration (µg/ml)	N (Control, Drug)	Rate (%)	Resting Potential (Δ; mV)	Overshoot (Δ; mV)	AP Height (Δ; mV)	APD <sub>50</sub> (Δ; msec)	dV/dt <sub>max</sub> (%)
<b>Bupivacaine</b>							
0.5	8, 7	96 ± 7	-0.8 ± 4.3	-0.6 ± 8.2	-0.2 ± 7.0	+6 ± 8	57 ± 29*
1.0	14, 5	93 ± 11	+0.7 ± 6.8	-6.0 ± 8.1	-6.7 ± 4.5*	-5 ± 9	57 ± 19*
1.75	5, 5	96 ± 2	-2.0 ± 8.4	-18.6 ± 12.4*	-16.6 ± 9.1*	+2 ± 12	34 ± 25*
1.75	5, 5	—	+9.0 ± 5.0*	-11.6 ± 9.1*	-20.6 ± 7.6*	+2 ± 7	41 ± 33*
2.5	7, 8	83 ± 14*	+0.3 ± 5.4	-8.6 ± 7.7*	-8.8 ± 5.6*	+16 ± 12*	17 ± 10*
2.5	13, 6	93 ± 4	-2.6 ± 4.7	-8.3 ± 9.4*	-7.7 ± 8.2*	+5 ± 22	46 ± 16*
3.5	4, 6	80 ± 11*	+2.5 ± 3.2	-9.8 ± 11.1*	-12.3 ± 10.7*	+11 ± 13	28 ± 23*
<b>Lidocaine</b>							
5	5, 7	110 ± 20*	-1.7 ± 3.5	-1.8 ± 5.9	-0.1 ± 4.8	-5 ± 9	106 ± 28
10	9, 7	91 ± 10*	+0.6 ± 8.1	-3.7 ± 11.7	-4.3 ± 8.4	-3 ± 5	56 ± 29*
17.5	6, 11	86 ± 7*	-0.6 ± 5.6	-6.6 ± 8.2	-6.5 ± 7.6*	+16 ± 8*	38 ± 18*
25	9, 9	84 ± 9*	-0.5 ± 3.9	-7.4 ± 7.4*	-4.9 ± 8.6	-6 ± 15	48 ± 34*
25	13, 8	93 ± 3	-0.6 ± 6.7	-9.3 ± 11.6*	-8.7 ± 9.4*	+2 ± 24	53 ± 23*
35	11, 6	89 ± 10*	-4.2 ± 6.4	-12.0 ± 10.2*	-7.8 ± 7.9*	+11 ± 12	38 ± 23*

Each row represents data from a single preparation; the Ns denote the number of APs analyzed for control and drug conditions. Means ± S.D. The standard deviations are calculated by error propagation formulae. Δ represents results expressed as a difference from control,

% as a percent of control.

\* Denotes results which represent a significant difference ( $P < 0.05$ ) from control within the individual experiment.

caine was sino-atrial (SA) block. Others have observed similar phenomena in the presence of local anesthetics. Mandel and Bigger<sup>23</sup> note several occurrences of SA block in isolated rabbit atria at approximately 21 µg/ml lidocaine. Parameswaran *et al.*<sup>24</sup> have shown in isolated rabbit heart that incomplete SA block can occur with lidocaine 10 µg/ml. Wojtczak *et al.*<sup>25</sup> also note that SA block was frequent with bupivacaine in isolated rabbit atria. Our study quantitates this finding and sheds light on its mechanism.

In our preparations which exhibited SA block, areas of apparently normal sinus node APs were recorded. However, the APs of transitional cells surrounding the sinus node were altered by lidocaine and bupivacaine. One of the changes was a reduction in the maximum rate of depolarization (statistical significance achieved with bupivacaine only), which is likely due to fast Na channel blockade. This attenuation of the transitional cell AP by lidocaine and bupivacaine may result in transmission of an electrical impulse insufficient to ex-

TABLE 5. Action Potential Characteristics in Septum (Rate Corrected)

Concentration (µg/ml)	N <sub>b</sub>	N <sub>i</sub>	Rate (min <sup>-1</sup> )	Resting Potential (mV)	AP Height Plateau (mV)	APD <sub>50</sub> (msec)	dV/dt <sub>max</sub> (V/sec)
<b>Bupivacaine</b>							
0 (Control)	10	88	96.1	-76.2	93.9	178	171
1.0	2	11	—	-76.8	94.8	199*	98*
1.75	2	13	84.3	-77.8	92.0	191*	91*
2.5	2	21	—	-72.9	93.7	211*	86*
3.5	1	9	96.0	-74.3	96.1	184	41*
5.0	2	12	77.8	-77.8	97.1	179	66*
7.5	1	7	54.7	-73.6	88.0	188	32*
Standard deviation				4.2	4.8	12	37
Significance				.79	.74	.0001	.0001
<b>Lidocaine</b>							
0 (Control)	7	72	89.1	-77.5	93.3	178	162
10	2	11	97.2	-79.9	96.5	181	112*
17.5	1	7	96.6	-76.7	94.1	168	91*
25	2	7	78.2	-76.4	89.0	191	131
35	1	8	87.0	-75.2	95.8	173	127*
50	1	6	65.5	-79.7	94.8	142	92*
Standard deviation				5.0	4.8	14	46
Significance				.82	.21	.099	.0001

Abbreviations and significance as in table 3. The height of the spike of the AP could only be determined with reliability in control solution

and, therefore, is not shown in the table.

\* Significantly different from control.

TABLE 6. Action Potential Characteristics in the Septum: Comparison to Controls from Individual Preparations

Concentration ( $\mu\text{g}/\text{ml}$ )	N (Control Drug)	Rate (%)	Resting Potential ( $\Delta$ ; mV)	AP Height Plateau ( $\Delta$ ; mV)	APD <sub>50</sub> ( $\Delta$ ; msec)	dV/dt <sub>max</sub> (%)
<b>Bupivacaine</b>						
1.0	11, 6	—	-0.5 $\pm$ 5.7	0.0 $\pm$ 8.8	+27 $\pm$ 16*	57 $\pm$ 15*
1.75	13, 5	90 $\pm$ 14	+1.0 $\pm$ 8.5	-5.1 $\pm$ 4.9*	+21 $\pm$ 16*	39 $\pm$ 14*
1.75	9, 8	100 $\pm$ 0	+0.1 $\pm$ 3.0	+1.2 $\pm$ 3.5	+5 $\pm$ 9	71 $\pm$ 19*
2.5	11, 19	—	-2.8 $\pm$ 6.5	-0.3 $\pm$ 5.8	+18 $\pm$ 12*	41 $\pm$ 15*
3.5	8, 9	98 $\pm$ 5	-0.3 $\pm$ 2.8	+2.4 $\pm$ 5.5	+18 $\pm$ 9*	25 $\pm$ 15*
5.0	11, 4	92 $\pm$ 14	+0.1 $\pm$ 5.1	-4.2 $\pm$ 5.7	+8 $\pm$ 11	30 $\pm$ 9*
5.0	7, 8	78 $\pm$ 6*	-2.8 $\pm$ 4.6	+4.9 $\pm$ 4.8*	+19 $\pm$ 4*	41 $\pm$ 13*
<b>Lidocaine</b>						
10	12, 8	100 $\pm$ 1	+0.6 $\pm$ 7.5	+0.7 $\pm$ 6.5	+2 $\pm$ 20	55 $\pm$ 27*
17.5	11, 7	100 $\pm$ 1	+0.9 $\pm$ 6.4	-1.4 $\pm$ 6.0	+2 $\pm$ 10	83 $\pm$ 49
25	12, 5	102 $\pm$ 14	-1.2 $\pm$ 7.0	-0.1 $\pm$ 6.2	+3 $\pm$ 14	85 $\pm$ 34
35	16, 8	103 $\pm$ 6	+0.8 $\pm$ 5.1	+1.3 $\pm$ 4.5	-5 $\pm$ 14	84 $\pm$ 21
50	7, 6	77 $\pm$ 7*	-0.7 $\pm$ 6.4	-1.7 $\pm$ 5.7	-10 $\pm$ 6	70 $\pm$ 18*

Abbreviations and symbols as defined in table 4.

\* Denotes results which represent a significant difference ( $P < 0.05$ )

cite atrial working muscle cells and, thus, produce sinus exit block. An increase in the threshold potential of atrial muscle cells could also contribute to such a block. However, the importance of effects on transitional cell APs was also demonstrated in hearts which did not develop complete SA block. Alternating AP configurations near the sinus node, which in one preparation correlated with 2-to-1 SA block, illustrate the graded efficacy of the transitional cell impulse. That is, the more attenuated AP did not produce atrial working muscle activity, while the less attenuated AP was adequate to do so. Cells exhibiting compound APs in or near the transitional regions of hearts exposed to lidocaine or bupivacaine, but which did not develop SA block, demonstrate drastically slowed or locally blocked conduction in this region. These aberrations would likely progress to complete SA block at higher drug concentrations.

The reversal of SA block by norepinephrine may reflect augmentation of the slow inward current, a well-known action of beta adrenergic agonists.<sup>26</sup> That is, the

from the control group within the experiment.

cells of the atrium become capable of producing regenerative APs based on this augmented slow inward current and independent of the fast sodium channel blocked by the local anesthetics. Such APs have been demonstrated in other cardiac tissues treated with catecholamines after blockade of fast sodium channels by means other than local anesthetics.<sup>27</sup>

#### ATRIO-VENTRICULAR CONDUCTION

In our study, atrial quiescence with lidocaine or bupivacaine occurred without prior AV block, and electrical activity in the AV node was conducted to the septum, but did not produce excitation of the atrium. Localized blocks and bizarre conduction patterns developed within the AV node, conditions which predispose to re-entrant arrhythmias. Indeed, in several preparations, premature septal beats could be shown to arise from the AV node, with re-entry being the likely mechanism of the extra beats.

#### ACTION POTENTIAL CHARACTERISTICS

Responses of atrial muscle APs to lidocaine and bupivacaine were similar. The major changes were reductions in the AP height and maximum rate of depolarization. Such effects are consistent with the sodium-channel-blocking properties of lidocaine and bupivacaine, and are also in agreement with the work of others using lidocaine in isolated atrial tissue. The high potency ratio for these effects illustrates that bupivacaine is much more potent than lidocaine (about 20 times) in depressing AP properties in atrial cells.

In septal cells, the changes in AP configuration were more variable. Reduction of the initial spike was observed with both lidocaine and bupivacaine. However,

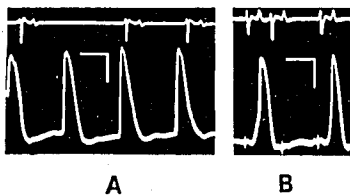


FIG. 9. Septal electrogram (upper trace) and action potentials from AV node region (lower trace) demonstrating arrhythmias generated in the AV node region. A. Bupivacaine 5  $\mu\text{g}/\text{ml}$ . The atrium is quiescent and regular spontaneous activity is apparently arising in the AV node and being conducted to the septum, but with a Wenckebach type block. B. Lidocaine 17.5  $\mu\text{g}/\text{ml}$ . The atrium is quiescent and the septum is being driven by a stimulator. AV node action potentials follow the septal beats. However, a premature septal beat occurs which apparently blocks capture or conduction of the next stimulator impulse.

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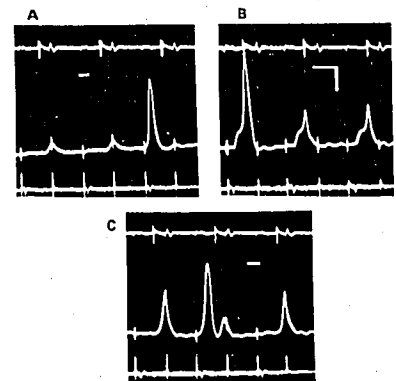
the reduction of the maximum rate of depolarization was more pronounced with bupivacaine, similar to the results of Lynch<sup>22</sup> in guinea pig papillary muscle. Resting potential and plateau potential were not changed by either drug in our experiments. AP duration showed a trend towards lengthening with bupivacaine, but little change with lidocaine. The increase in duration with bupivacaine exceeded that expected on the basis of concomitant decreases in heart rate. A Purkinje fiber taken from one of our dogs and bathed in the solution used for perfusion clearly showed a decrease in AP duration with bupivacaine 1.75  $\mu\text{g}/\text{ml}$ . Thus, the increase in duration in septal cells does not represent a generalized AP lengthening in these preparations. The shortening of the Purkinje fiber AP in lidocaine is well described.<sup>28</sup>

Several implications follow from the ventricular muscle AP lengthening found with bupivacaine. A ventricular tachycardia consistent with Torsades de Pointes has been observed in bupivacaine-treated hearts.<sup>29</sup> This arrhythmia is also associated with other drugs, such as quinidine, which lengthen the ventricular AP. Second, the divergent AP duration effects between Purkinje fiber and ventricular muscle may create an increased temporal dispersion of repolarization, a situation which may be associated with ventricular fibrillation<sup>30</sup> and Torsades de Pointes.<sup>31</sup>

#### DIFFERENCES BETWEEN LIDOCAINE AND BUPIVACAINE

We conclude that the differences between lidocaine and bupivacaine are, for the most part, quantitative rather than qualitative. That is, for nearly all of the endpoints measured in this study, both drugs produce the same effects, but bupivacaine is clearly more potent. With the possible exception of depression of heart rate, bupivacaine's potency for cardiac end-points relative to lidocaine's far exceeds its relative potency for neural blockade. Several reasons for the high potency of bupivacaine relative to lidocaine for depression of cardiac conduction have been discussed in detail by Clarkson and Hondeghem.<sup>14</sup> They have shown that bupivacaine not only has greater affinity for cardiac sodium channels than lidocaine, but the drugs also differ in their kinetics of association to and dissociation from the channels. At physiologic heart rates and high bupivacaine concentrations (comparable to the rates and concentrations used in the present study), the drug will tend to associate with cardiac sodium channels relatively rapidly, but dissociate slowly leading to an accumulation of blocked channels, a situation less likely to occur with the rapidly dissociating drug, lidocaine. The rate of cardiac conduction is highly dependent on the maximum rate of depolarization of the action potential, which, in turn, is a function of the number of open sodium chan-

FIG. 10. Septal electrograms (top traces), action potentials from the AV node region (middle traces), and atrial electrograms (bottom traces) from a preparation exposed to bupivacaine 3.5  $\mu\text{g}/\text{ml}$ . The atrium is being stimulated, and every other stimulator impulse results in capture. The stimulation artifacts are seen best as the most prominent deflections of the lowest trace in each panel. Atrial activity is marked by the small downward deflections following every other stimulator artifact on the bottom traces. Septal electrical activity is represented by the sharp spikes on the upper traces. (The broader deflections in the upper traces following these spikes are motion artifacts.) The middle trace of panel A represents a cell in the AV node which fires between atrial and septal activity, but not consistently. Panel B illustrates a similar phenomenon, but this AV node cell fires at the time of septal activity. Panel C illustrates a cell which fires once in the proper sequence between atrium and septum, and which also produces attenuated APs after septal activation. Calibration bars (shown in Panel B): horizontal = 200 msec; vertical = 20 mV for middle traces. Position of horizontal bars marks 0 mV for middle traces.



nels. Differences in the potency between lidocaine and bupivacaine for sodium channel blockade are, thus, reflected in end-points related to conduction. Contractility and pacemaker function are not directly determined by sodium current, and local anesthetic effects on these end-points may be related to mechanisms other than blockade of sodium channels. The markedly lower potency ratios for contractility and rate (compared to cardiac conduction) indeed suggest that an action other than sodium channel blockade is important.

In intact animals, the EKG abnormalities and arrhythmias related to depression of conduction (widened QRS, increased PR interval, AV blocks, asystole) can be readily explained on the basis of electrophysiologic observations in isolated tissue. One might predict that these same phenomena should be more often reported with lidocaine, since it produced most of the same electrophysiologic effects as bupivacaine. Possible explanations are that neurogenic events mask certain direct effects of lidocaine, or that depression of heart rate and contractility intervene before conduction disturbances become apparent.

With respect to tachyarrhythmias, both drugs create conditions which would promote re-entrant rhythms, particularly in the regions of the sinus and AV nodes. Bupivacaine's lengthening of the AP in septal cells may also play a role in the generation of ventricular tachyarrhythmias, and could represent an important point of

difference with lidocaine. Extracardiac drug effects may also be relevant, as Heavner<sup>32</sup> has provided evidence that actions of bupivacaine on the central nervous system of cats can induce ventricular arrhythmias independent of direct cardiac effects. Such effects were not found with lidocaine. Thomas *et al.*<sup>33</sup> have presented a similar hypothesis based on rat studies, although they did not see as profound a difference between lidocaine and bupivacaine injected into the CNS. Thus, bupivacaine-induced arrhythmias may be related to the following factors or their interaction: 1) profound depression of cardiac conduction and excitability; 2) changes in repolarization patterns within ventricular muscle and Purkinje fibers; and 3) alterations in autonomic neural activity triggered by large amounts of bupivacaine in the CNS.

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