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Severe Hypoxia Enhances Central Nervous System and Cardiovascular Toxicity of Bupivacaine in Lightly Anesthetized Pigs

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Toxic systemic reactions to bupivacaine usually involve a number of factors, including hypoxia and acidosis. The objective of this study was to test the hypothesis that cardiovascular and central nervous system responses to bupivacaine overdose are proportional to the severity of hypoxia. The central nervous system and cardiovascular toxicity of bupivacaine was examined in three groups of pigs breathing 30%, 15%, or 10% O_2, 70% N_2O, and He (FI_{O_2} = 0.15 and 0.1 groups). The 18 2-week-old pigs (6 animals per treatment) were paralyzed with pancuronium and their lungs ventilated mechanically. During the intravenous infusion of bupivacaine 2 $mg \cdot kg^{-1} \cdot min^{-1}$, four readily identified toxic endpoints (seizures, arrhythmias, isoelectric electroencephalogram, asystole) were observed in all animals, with the exception that 1 pig in the FI_{O_2} = 0.3 group and 1 in the FI_{O_2} = 0.15 group had no arrhythmias. Bupivacaine doses producing seizures, isoelectric EEG, and asystole were significantly less in the FI_{O_2} = 0.1 groups as compared to the other groups. Arrhythmias occurred before seizures in all animals in the FI_{O_2} = 0.1 group but in only 1 of 5 and 2 of 5 animals in the FI_{O_2} = 0.15 and 0.3 groups, respectively. There was no significant difference between the arrhythmic dose of bupivacaine in the FI_{O_2} = 0.3 *versus* 0.1 animals (8.4 ± 2.4 *vs.* 4.0 ± 1.4 $mg \cdot kg^{-1}$), but the dose was significantly less in the FI_{O_2} = 0.1 animals than in the FI_{O_2} = 0.15 animals (12.5 ± 5.6 $mg \cdot kg^{-1}$). Arterial *p*H was stable in all three groups during bupivacaine infusion. Pa_{CO_2} decreased in all three groups, and Pa_{O_2} increased in the FI_{O_2} = 0.15 and 0.1 groups. As bupivacaine infusion time increased, heart rate in all groups decreased (significant change over time), and the rate of decrease was significantly different (FI_{O_2} = 0.1 > FI_{O_2} = 0.15 > FI_{O_2} = 0.3). In the FI_{O_2} = 0.3 group, mean blood pressure first increased and then decreased as bupivacaine infusion time increased (significant rate of change, FI_{O_2} = 0.1 > FI_{O_2} = 0.3 > FI_{O_2} = 0.15). These results apparently contradict *in vitro* findings that neither hypoxia nor acidosis alone potentiates bupivacaine cardiotoxicity but that together they do. However, metabolic as well as respiratory acidosis plus hypoxia probably was present at the cellular level in severely hypoxic pigs. We conclude that severe (Pa_{O_2} < 40 mmHg) but not borderline moderate (Pa_{O_2} 40–62 mmHg) hypoxia increases the likelihood that bupivacaine will induce arrhythmias before seizures, and enhances the central nervous system and cardiovascular toxicity of bupivacaine. (Key words: Anesthetics, local: bupivacaine. Toxicity: local anesthetic. Hypoxia. Central nervous system: isoelectric EEG; seizures. Cardiovascular system: arrhythmias; asystole.

SIDE EFFECTS of local anesthetic indicating toxicity include cardiac arrhythmias and grand mal seizures. Data from animals and humans indicate that bupivacaine-induced convulsions are accompanied by hypoxia, hypercapnia, and acidosis.[1] Rosen *et al.*[2] demonstrated in sheep that hypercapnia, acidosis, and hypoxia enhance bupivacaine cardiotoxicity. *In vitro,* neither hypoxia nor metabolic or respiratory acidosis alone enhanced atrial depression caused by local anesthetics, whereas conditions simulating combined hypoxia/acidosis greatly enhanced bupivacaine-induced cardiac depression.[3] *In vivo,* however, compensatory responses to hypoxia (*e.g.*, central sympathetic stimulation[4]) coupled with centrally mediated effects of bupivacaine on heart rhythm[5] may influence cardiovascular responses to intravenously administered bupivacaine. Moreover, we hypothesize that the severity (and possibly the nature) of the central nervous system and cardiovascular responses to bupivacaine overdose is proportional to the degree of hypoxia. To test this possibility, we compared the threshold doses of bupivacaine required to produce arrhythmias, seizures, isoelectric electroencephalogram (EEG), and asystole in young pigs, the lungs of which were ventilated with an FI_{O_2} of 0.3, 0.15, or 0.1.

Materials and Methods

After Animal Care and Use Committee approval, we studied 20 2-week-old, farm-bred pigs weighing 5.2 ± 1.08 kg. The pigs were transported from the farm to the laboratory and studied the same day. Anesthesia was induced using halothane by face mask, and a tracheal tube was inserted *via* tracheostomy. Ventilation was maintained with a Siemens-Elema 900D ventilator. End-tidal CO_2, sampled from the distal end of the tracheal tube, was

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measured with a Cavitron infrared CO_2 analyzer. Using end-tidal CO_2 as a guide, we adjusted ventilation as needed to maintain arterial CO_2 (Pa_{CO_2}) near 35 mmHg during the control period. Electrocardiogram (ECG) leads I, II, and modified V1 and frontooccipital EEG were recorded continuously on a strip chart. Body temperature was measured rectally and maintained between 36° C and 38° C using a heating pad.

During surgical procedures, anesthesia was maintained using 1.5–2% inspired halothane concentration. Surgical preparation included: 1) insertion of a catheter into the right femoral artery to monitor arterial blood pressure and to sample blood for gas analysis; 2) insertion of a catheter into the right femoral vein to measure plasma bupivacaine concentrations; and 3) insertion of a catheter into the abdominal vena cava near the diaphragm *via* the left femoral vein for bupivacaine infusion.

When surgical preparation was completed, halothane was discontinued, and all pigs were given 25 $ml \cdot kg^{-1}$ lactated Ringer's solution and 0.1 $mg \cdot kg^{-1}$ pancuronium intravenously. Neuromuscular blockade was maintained as needed with additional pancuronium so that recorded seizure activity on the EEG was accompanied by slight twitching of the extremities. Pancuronium produced a transient increase in heart rate and blood pressure followed in some cases by a transient decrease in blood pressure. Pigs were divided into three treatment groups (six per group) and an hypoxia control group (HCG; n = 2). The fraction of O_2 (FI_{O_2}) in the inspired gas mixture for group A was maintained at 0.3 (70% N_2O/30% O_2) for 30 min to allow stabilization before the infusion phase of the experiment (see below) was begun. FI_{O_2} was maintained at 0.3 for 15 min in groups B, C, and HCG and then reduced to 0.15 (70% N_2O, 15% O_2, 15% He) in group B and to 0.1 (70% N_2O, 10% O_2, 20% He) in groups C and HCG. Fifteen minutes later, bupivacaine (or saline, in group HCG) infusion was started. In all groups, baseline blood gas samples were drawn before bupivacaine or saline infusion was begun.

During the infusion phase, all pigs were maintained at their respective FI_{O_2} while bupivacaine (or saline, in group HCG) was infused continuously at 1 $mg \cdot kg^{-1} \cdot min^{-1}$ with an infusion pump. Saline infusion in HCG pigs was set at the rate fluid would be given during bupivacaine administration. Threshold doses of bupivacaine were recorded for each of four events: 1) first dysrhythmia, 2) first seizure, 3) isoelectric EEG, and 4) asystole. Saline infusion was continued for 30 min in the HCG; then anesthesia was deepened (4% halothane), and the animals were killed with an intravenous bolus of saturated KCl. Dysrhythmia was defined as an abrupt change in rhythm and electrical signal configuration on the ECG, accompanied by an abrupt change in arterial pulse pressure. Seizure was defined as the appearance of epileptiform activity on the EEG. Asystole was defined as absence of a QRS complex on the ECG and absence of a pressure pulse on the arterial blood pressure trace.

Every 5 min during the infusion, an arterial blood sample (0.3 ml) was drawn to measure *p*Ha, Pa_{CO_2}, and Pa_{O_2}, and a venous blood sample (0.5 ml) was drawn to measure bupivacaine concentration. Plasma bupivacaine concentrations were determined by high-performance liquid chromatography (ultraviolet detection at 210 nm[6]; sensitivity < 0.1 $\mu g \cdot ml^{-1}$; coefficient of variation at 10 $\mu g \cdot ml^{-1}$ < 3%). End-tidal CO_2, EEG, ECG, rectal temperature, and arterial blood pressure and O_2 saturation were recorded continuously.

Results were expressed as mean ± standard deviation. Statistical significance was accepted if $P \leq 0.5$. One way analysis of variance and the Student-Newman-Keuls test were used to compare the differences among the groups for plasma concentrations and threshold doses of bupivacaine, baseline values for mean blood pressure, heart rate, and arterial blood gas tensions, and differences within groups for threshold doses of bupivacaine. Chi-square proportional analysis was used to test for significant differences between groups with respect to the occurrence of arrhythmias before seizures. Multiple analysis of variance and exact F test statistics were used to compare heart rate, blood pressure, Pa_{CO_2}, base excess, Pa_{O_2}, HCO_3, and *p*H changes *versus* time for the three treatment groups.

Results

Blood Gas Data

Pa_{CO_2} values for the three bupivacaine treatment groups of animals were not significantly different just prior to bupivacaine infusion (table 1), but Pa_{O_2} values were different, as expected. Base deficit was significantly greater in the FI_{O_2} = 0.1 group compared to the FI_{O_2} = 0.15 but not compared to the FI_{O_2} = 0.3 group. Although arterial *p*H was significantly less in the FI_{O_2} = 0.1 group as compared to the FI_{O_2} = 0.15 group, the difference was only 0.06 *p*H units, and pH_a values were in normal range. Arterial *p*H before and after the FI_{O_2} was decreased to target level for the FI_{O_2} = 0.15 and 0.1 groups were similar (FI_{O_2} = 0.15, 7.44 *vs.* 7.48; FI_{O_2} = 0.1, 7.44 *vs.* 7.42). Blood gas values for the FI_{O_2} = 0.1 and HCG pigs before infusion was started were similar (table 1).

During bupivacaine infusion, arterial *p*H remained in a relatively narrow range for the treatment groups (table 1). Pa_{CO_2} decreased (significant change over time) in all three groups but not at a significantly different rate. Pa_{O_2} increased in the FI_{O_2} = 0.15 and 0.1 groups at significantly different rates (FI_{O_2} = 0.1 < FI_{O_2} ± 0.15). The pH_a of the saline control group progressively decreased during the 30-min infusion period (pH_a = 7.41 at time 0

TABLE 1. Blood Gas Values *versus* Time

	0	5	10	15	20 (n = 5)	25 (n = 4)	30 (n = 2)
FI_{O_2} = 0.3							
*p*Ha	7.45 (0.02)	7.48 (0.02)	7.49 (0.03)	7.46 (0.03)	7.47 (0.04)	7.48 (0.04)	7.49 (0.07)
Pa_{CO_2}	30 (4.4)	27 (1.9)	25 (4.7)	25 (4.8)	27 (1.9)	23 (1.7)	26 (0.8)
Pa_{O_2}	91 (29.8)	112 (19.7)	99 (20.8)	104 (19.3)	98 (22.1)	118 (13.7)	106 (15.6)
HCO_3	21 (3.1)	20 (4.3)	19 (4.3)	18 (3.6)	20 (2.9)	18 (2.0)	20 (2.5)
BE	−1.5 (2.7)	−1.1 (1.5)	−1.1 (3.9)	−3.2 (3.0)	−1.4 (3.4)	−2.9 (2.7)	−1.0 (3.8)
					(n = 5)	(n = 3)	(n = 3)
FI_{O_2} = 0.15							
*p*Ha	7.48 (0.03)	7.5 (0.03)	7.51 (0.03)	7.51 (0.03)	7.52 (0.03)	7.52 (0.06)	7.53 (0.05)
Pa_{CO_2}	29 (3.8)	28 (4.6)	27 (4.0)	26 (2.7)	25 (2.8)	21 (5.4)	21 (2.8)
Pa_{O_2}	40 (7.6)	42 (7.8)	41 (7.1)	46 (6.2)	51 (8.1)	60 (14.0)	62 (11.1)
HCO_3	22 (2.1)	21 (2.4)	21 (1.9)	21 (1.1)	20 (1.1)	17 (2)	17 (0.6)
BE	0.2 (1.7)	0.6 (1.4)	0.6 (0.9)	0.5 (0.7)	0 (0.9)	−2.3 (0.2)	−1.8 (0.9)
					(n = 4)		
FI_{O_2} = 0.1							
*p*Ha	7.42 (0.04)	7.42 (0.05)	7.41 (0.04)	7.41 (0.06)	7.42 (0.09)		
Pa_{CO_2}	30 (2.9)	26 (3.6)	24 (3.9)	24 (4.4)	19 (3.2)		
Pa_{O_2}	25 (1.7)	30 (3.4)	34 (5.7)	35 (4.2)	42 (4.8)		
HCO_3	19 (2.1)	17 (2.9)	15 (2.6)	15 (1.6)	12 (1.2)		
BE	−3.4 (2.4)	−5.2 (3.3)	−6.6 (2.5)	−6.9 (2.0)	−8.8 (3.1)		
	HCG	(n = 2)					
FI_{O_2} = 0.1 (HCG)							
*p*Ha	7.41	7.38	7.35	7.31	7.32		7.28
Pa_{CO_2}	29	29	27	26	27		27
Pa_{O_2}	26	25	27	27	27		29
HCO_3	18	17	14	13	13		13
BE	−4.2	−6.2	−9.0	−11.3	−10.5		−12.1

Standard deviations are shown in parentheses.

BE = base excess; HCG = hypoxia control group.

and 7.28 at 30 min). Pa_{CO_2} and Pa_{O_2} in the two animals in this group remained in a narrow range, whereas HCO_3 decreased and base excess became progressively more negative during saline infusion. Calculated HCO_3 and base excess did not vary in the FI_{O_2} = 0.3 treatment group for the duration of the study, whereas values for the FI_{O_2} = 0.15 group decreased after 25 min. In contrast, the HCO_3 and base excess values decreased as bupivacaine infusion time increased in the FI_{O_2} = 0.1 group. The differences in base excess values, but not HCO_3 values, *versus* time for the three groups were significantly different.

Heart Rate and Blood Pressure

Heart rate before bupivacaine infusion began was significantly higher in animals whose lungs were ventilated with FI_{O_2} = 0.15 or 0.1 as compared to animals whose lungs were ventilated with FI_{O_2} = 0.3 (fig. 1). Conversely, mean blood pressures in the three groups of animals were not different before the start of bupivacaine (fig. 2).

As bupivacaine infusion time increased, heart rate in all groups decreased (significant change over time), and the rate of decrease was significantly different (FI_{O_2} = 0.1 > FI_{O_2} = 0.15 > FI_{O_2} = 0.3). In the FI_{O_2} = 0.3 group, mean blood pressure first increased and then decreased (fig. 2). In the other two groups, blood pressure decreased as bupivacaine infusion time increased. The rate of change

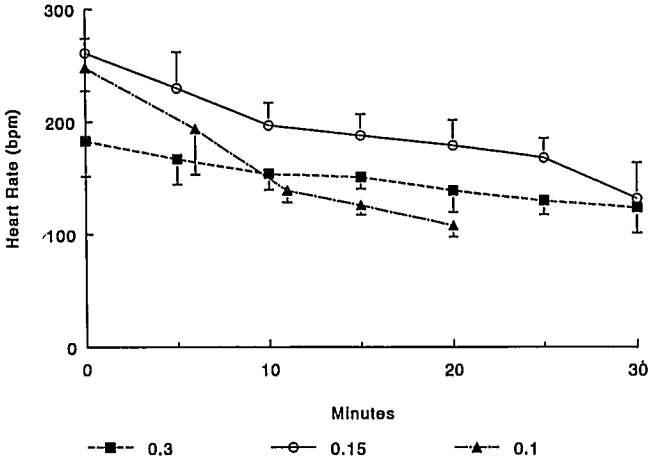

FIG. 1. Heart rate (mean ± SD) *versus* bupivacaine infusion time for the three treatment groups.

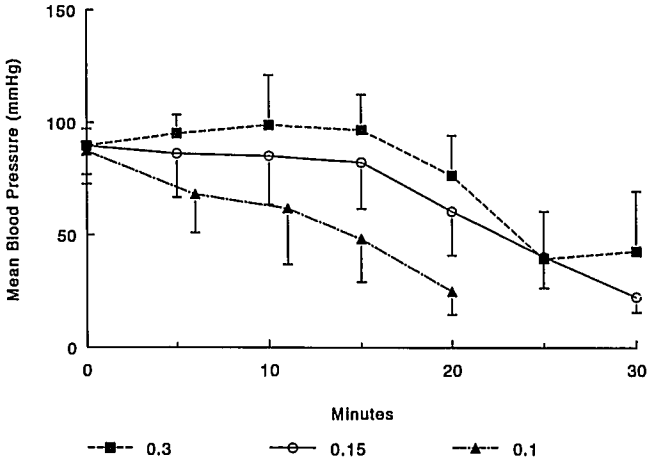

FIG. 2. Mean blood pressure (average ± SD) *versus* bupivacaine infusion time for the three treatment groups.

over time was significant and different according to group (FI_{O_2} = 0.1 > FI_{O_2} = 0.3 > FI_{O_2} = 0.15).

Mean blood pressure and heart rate in the saline group were similar to those of the FI_{O_2} = 0.1 group just before infusion was started. Blood pressure and heart rate in the saline controls remained in a narrow range during saline infusion.

Toxic Endpoints

No seizures or arrhythmias were observed in the stabilization period prior to bupivacaine administration. No seizures were observed in the saline control group, and one or two junctional beats were observed between 21 and 23 min after saline infusion started.

All four toxic endpoints (seizure, arrhythmia, isoelectric electroencephalogram, asystole) were observed in all animals, with the exception that one pig in the FI_{O_2} = 0.3 group and one in the FI_{O_2} = 0.15 group had no dysrhythmia. Doses of bupivacaine required to produce toxic endpoints were not significantly different for the FI_{O_2} = 0.3 and 0.15 groups (fig. 3). On the other hand, the doses of bupivacaine producing seizures, isoelectric electroencephalogram, and asystole were significantly less in the FI_{O_2} = 0.1 group as compared to the other two groups. The average dysrhythmia dose for the FI_{O_2} = 0.1 group was significantly less than it was for the FI_{O_2} = 0.15 group but not as compared to the dose for the FI_{O_2} = 0.3 group. No readily discernible differences in seizure pattern or type of arrhythmias were detected when records for the three treatment groups were compared. However, two of five of the FI_{O_2} = 0.3 animals had dysrhythmias before seizures, as did one of five animals in the FI_{O_2} = 0.15 group, whereas all animals in the FI_{O_2} = 0.1 group had dysrhythmias before seizures. The difference between the frequency with which arrhythmias occurred before seizures is significant for the FI_{O_2} = 0.1 group as compared to the other groups. Within groups, however, the doses producing seizures and arrhythmias did not differ.

The first ECG change following the start of bupivacaine infusion was usually observed within 30 s and consisted of an increase in QRS amplitude and width. Usually the width and amplitude of the QRS complex continued to increase, and the P wave became undiscernible (perhaps merged with T wave). The pattern was judged to be a wide complex supraventricular tachycardia. The point identified as the onset of arrhythmia was where there was a pause (2:1 atrioventricular conduction block) followed by normal-appearing P, QRS, and T waves, with immediate return to a wide complex supraventricular tachycardia. This pattern eventually converted to sinus bradycardia and then asystole. Occasionally, ventricular beats and irregular sinus rates were observed. Electromechanical dissociation was not observed, and therefore conduction failure, not loss of pump function of the heart, was the terminal event.

Venous Bupivacaine Concentration

Venous plasma concentrations of bupivacaine did not differ significantly between groups for the sample times where comparable data were available (fig. 4; samples for all animals in all groups were available for up to 15 min; no animals in the FI_{O_2} = 0.1 group survived for 25 min; and no bupivacaine blood concentration values are available beyond 20 min for any animals in this group).

Discussion

Results of this study show that the doses of bupivacaine producing seizures, isoelectric EEG, and asystole are less,

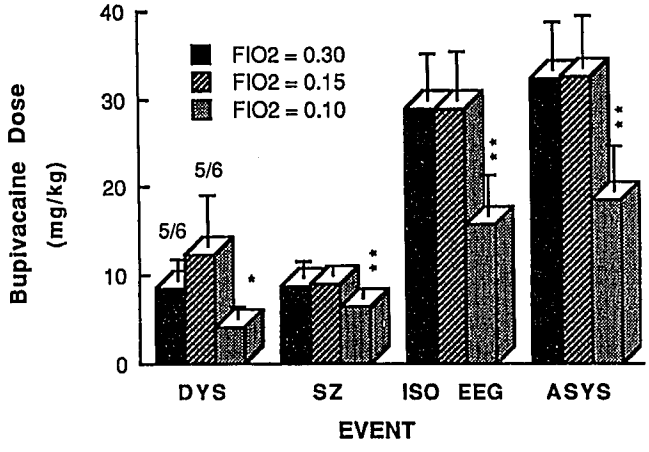

FIG. 3. Doses of bupivacaine (mean ± SD) required to produce each of the four toxic endpoints. *Significant difference between FI_{O_2} = 0.15 and 0.1. **Significant difference between FI_{O_2} = 0.1 and other two groups (5/6 indicates number of animals exhibiting endpoint *vs.* number of animals tested). DYS = dysrhythmia; SZ = seizure; ISO EEG = isoelectric electroencephalogram; ASYS = asystole.

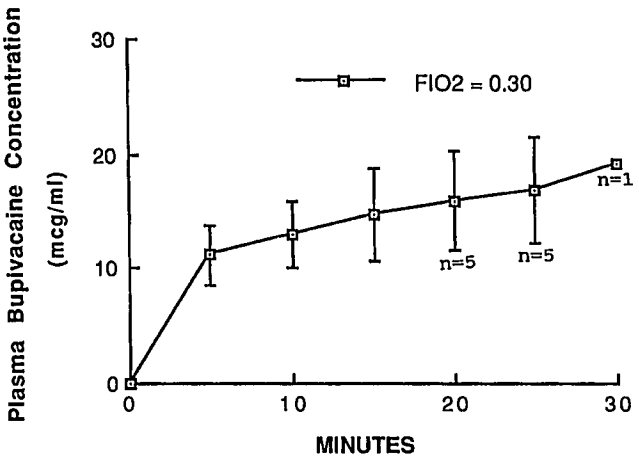

FIG. 4. Venous plasma bupivacaine concentration (mean ± SD) *versus* bupivacaine infusion time for the $F_{I_{O_2}} = 0.3$ group.

and the likelihood of arrhythmias occurring before seizures is greater, in severely hypoxic pigs than in moderately hypoxic or slightly hyperoxic pigs. For purposes of this discussion, hypoxia is defined using criteria applied to humans breathing room air (mild = $Pa_{O_2} < 80$ mmHg; moderate = $Pa_{O_2} < 60$ mmHg; and severe = $Pa_{O_2} < 40$ mmHg.[7]

Given that the plasma concentration of bupivacaine at each sampling time did not differ significantly among treatment groups, the pharmacokinetic behavior of bupivacaine in the different groups apparently was similar. Therefore, we concluded that differences in doses of bupivacaine required to produce toxic endpoints in the different groups of animals reflect pharmacodynamic and not pharmacokinetic differences. Our results appear to contradict results of *in vitro* studies showing that neither hypoxia nor acidosis alone enhances bupivacaine cardiotoxicity but that together they do.[3] However, blood gas data and hemodynamic changes during bupivacaine infusion suggests that, at the cellular level, both hypoxia and acidosis probably were present. If so, there is no dichotomy between our *in vivo* and the *in vitro* data. The blood gas data reveal a progressive alkalosis (decreasing Pa_{CO_2}) offset by a metabolic acidosis. Because tidal volume and respiratory rate were kept constant, reasons for the decrease in Pa_{CO_2}, other than ventilatory changes, must be considered. We hypothesize that the decrease in Pa_{CO_2} was due at least in part to reduced perfusion and hence less extraction of CO_2 from tissues. Reduced tissue blood flow would allow CO_2 and lactate to accumulate and would further decrease the delivery of O_2, producing respiratory and metabolic acidosis plus marked hypoxia at the cellular level. From a clinical perspective, these data suggest that hypercapnia associated with respiratory depression would increase the magnitude of acidosis produced by hypoxia and thereby add to the effects of hypoxia on bupivacaine toxicity. The increases in Pa_{O_2} we observed probably were due at least in part to a decrease in alveolar CO_2 offset by an increase in alveolar O_2. Our conclusions regarding pH_a and the changes in Pa_{CO_2} and Pa_{O_2} are supported by the data from our small control group. In that group, blood pressure, Pa_{O_2}, and Pa_{CO_2} remained stable over time, but pH_a gradually decreased.

A relative tachycardia in the hypoxic groups before bupivacaine infusion began indicates sympathetic activation. By contrast, the more rapid decrease in heart rate and blood pressure in the $F_{I_{O_2}} = 0.1$ animals as compared to the others indicates synergistic depressant effects of severe hypoxia and bupivacaine on the sinoatrial node as well as the contractile elements of the ventricles and resistance blood vessels.

There is reason to expect synergism between hypoxia and bupivacaine in the production of ventricular arrhythmias since both hypoxia and bupivacaine have been shown to be arrhythmogenic. However, hypoxia and bupivacaine have opposing electrophysiologic effects on heart tissue. *In vitro,* hypoxia plus metabolic blockade produce marked shortening of cardiac action potentials[8] and bupivacaine prolongs them.[9]

The spectrum of cardiac arrhythmias we observed indicate that under conditions of the study, the bundle conduction system is more sensitive than other parts of the heart to bupivacaine. However, it is interesting that asystole was usually preceded by sinus bradycardia, with relatively normal-appearing P, QRS, and T waves. Asystole usually consisted of sinus arrest or ventricular arrest followed by a short period during which only P waves were present. Apparently, hypoxia and bupivacaine depressed the electrical properties of the entire heart prior to asystole, but in some cases the most resilient part was the sinus node.

Human case reports and many animal studies have demonstrated that bupivacaine produces ventricular fibrillation (VF). However, this is not always the case. For instance, Feldman *et al.*[10] demonstrated that only two of six unpremedicated dogs developed VF after intravenous injection of two times the convulsant dose of bupivacaine, followed by resuscitation measures as soon as signs of systemic toxicity were observed. (No dogs given the convulsant dose developed VF.) Apparently, four of the dogs either were not predisposed to have VF, or injection of thiamylal and the initiation of respiratory support were adequate to prevent VF. Perhaps it is because ventilation was controlled and because the pigs were only lightly anesthetized during the bupivacaine injection that they did not develop VF. The relative importance of the light N_2O anesthesia *versus* controlled ventilation, if any, in preventing VF is unknown. While unproven, we believe a number of factors (*e.g.*, heart rate, level of consciousness,

level of sympathetic activity, rate of bupivacaine injection, acid–base status) acting together determine whether or not bupivacaine produces VF. The initial point at which we saw 2:1 atrioventricular block in our study presents a potentially important opportunity for ventricular cells (especially those with an increased level of automaticity) to gain control over heart rate and rhythm.

The decreased seizure threshold seen in the severely hypoxic animals is consistent with our interpretation of the acid–base status of these animals (tissue hypoxia and acidosis) and with others' reports regarding the effects of acid–base changes on local anesthetic seizure thresholds. According to de Jong, both metabolic and respiratory acidosis decrease local anesthetic seizure thresholds.[11]

Mechanical ventilation, administration of a neuromuscular blocking agent with vagolytic activity, light anesthesia, and age are known or suspected to affect systemic responses to bupivacaine overdose and must be considered when interpreting the outcome of our study. However, the conclusion that severe tissue hypoxia and acidosis enhance the cardiovascular and central nervous system toxicity of bupivacaine is consistent with results of animal experiments and clinical studies regarding toxic responses of humans to bupivacaine.

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