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Mechanisms of the Putative Cardioprotective Effect of Hexamethonium in Anesthetized Dogs Given a Large Dose of Bupivacaine

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Background: **Some reports suggest that activation of the autonomic nervous system by bupivacaine could participate in its cardiotoxicity. This is based in part on the fact that hexamethonium suppresses cardiac disturbances in anesthetized rabbits given small intracerebroventricular doses of bupivacaine. The aims of the current study were to determine, in anesthetized dogs, (1) whether the activation of the autonomic nervous system is deleterious after a large intravenous dose of bupivacaine and (2) whether the parasympathetic or sympathetic system is implicated in the bupivacaine-induced deleterious activation of the autonomic nervous system.**

Methods: **We used an electrophysiologic model in closed-chest dogs anesthetized with sodium pentobarbital. In group 1 (n = 6), dogs were given 4 mg/kg intravenous bupivacaine over 10 s. In group 2 (n = 6), dogs were given the same dose of bupivacaine 5 min after having received 0.2 mg/kg intravenous atropine sulfate. In group 3 (n = 9), dogs were pretreated with 10 mg/kg intravenous hexamethonium and then given bupivacaine 4 mg/kg. In addition, in group 3, the right atrium was paced at a basic cycle length of 400 ms to obtain a heart rate similar to that of group 1.**

Results: **Bupivacaine in group 1 induced significant bradycardia; lengthening of PR, atria–His, His–ventricle, and QTc intervals; and QRS widening. The first derivative of left ventricular pressure was significantly decreased, whereas left ventricular end-diastolic pressure was increased. Atropine pretreatment did not modify cardiac disturbances induced by bupivacaine. Hexamethonium pretreatment induced significantly less QRS widening and QTc lengthening than was seen in group 1 but worsened the bupivacaine effects on bradycardia, atria–His and PR intervals, mean aortic pressure, and first derivative of left ventricular pressure. Moreover, atrial pacing in group 3 induced alterations of QRS similar to those in group 1.**

Conclusions: **Considering that marked slowing of ventricular conduction velocity (*i.e.*, QRS widening) is known to facilitate reentrant ventricular arrhythmias, we conclude that (1) the activation of the autonomic nervous system by bupivacaine is not as deleterious as previously suggested; (2) the parasympathetic system is not markedly implicated in the worsening of direct bupivacaine cardiotoxicity; and (3) the sympathetic nervous system acts only by inducing a less marked bradycardia, which slows ventricular conduction velocity in a use-dependent manner, facilitating reentrant arrhythmias. (Key words: Anesthetics, local: bupivacaine. Monitoring: electrophysiology. Parasympathetic nervous system: atropine. Sympathetic nervous system: hexamethonium. Toxicity: bupivacaine.)**

This article is accompanied by a Highlight. Please see this issue of ANESTHESIOLOGY, page 27A.

SEVERAL mechanisms explain the cardiac events induced by bupivacaine (cardiovascular collapse, extreme bradycardia, atrioventricular and intraventricular blocks, or ventricular arrhythmias) when there is a sudden and large increase in its plasma concentration, as in case of accidental intravascular injection. In particular, from an electrophysiologic point of view, it has been demonstrated that bupivacaine impairs the $\dot{V}_{max}$ of fast action potentials by blocking the sodium channels in their inactivated state in a fast-in–

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slow-out fashion.[1] Moreover, bupivacaine inhibits several other cardiac electrophysiologic currents, such as the transient outward potassium current,[2] the delayed outward potassium current,[3] and the calcium-inward current.[4–7] We previously demonstrated in isolated rabbit heart that bupivacaine slows ventricular conduction velocities in a dose- and use-dependent manner, inducing functional arcs of ventricular conduction blocks that facilitate the occurrence of ventricular arrhythmias by reentry.[8] These alterations are caused mainly by the inhibition of the fast-inward sodium current, which could explain the electrocardiographic impairment induced by a toxic dose of bupivacaine.[9–11] We also have reported that, in anesthetized dogs, marked lengthening of PR and His–ventricle (HV) intervals and QRS widening are the major electrocardiographic alterations induced by a large dose of bupivacaine.[11]

From an hemodynamic point of view, bupivacaine is a marked cardiodepressant drug. Many studies have reported that bupivacaine induces a dramatic decrease in myocardial contractility.[4,12–14] For example, we reported in anesthetized dogs that the administration of an intravenous (iv) bolus of 4 mg/kg bupivacaine induces a marked decrease in the first derivative of left ventricular pressure ($LVdP/dt_{max}$).[11] Thus, the direct alteration of cardiac electrophysiology and contractility induced by bupivacaine can explain the cardiotoxic accidents. Nevertheless, two reports suggest that bupivacaine cardiotoxicity is also mediated by the autonomic nervous system.[15,16] These studies demonstrated that cardiotoxicity could be induced in rabbits and cats by administering small doses of bupivacaine in the nucleus tractus solitarius or in the lateral cerebral ventricle.

More recently, Bernards and Artru[17] confirmed in halothane-anesthetized rabbits that the intracerebroventricular administration of small doses of bupivacaine induced hypertension and cardiac arrhythmias. Moreover, the intracerebroventricular administration of midazolam, known to potentiate the activity of γ-aminobutyric acid–ergic neurons that inhibit the activity of outflow neurons of the autonomic nervous system, suppressed bupivacaine-induced hypertension and arrhythmias. Similarly, these authors demonstrated that the iv administration of hexamethonium, a ganglioplegic drug, also suppressed bupivacaine-induced cardiac disturbances. Bernards and Artru[17] concluded that activation of the autonomic nervous system by bupivacaine participates in the direct cardiotoxicity of the drug. Nevertheless, these authors were not able to determine (1) whether the parasympathetic system or the sympathetic system or both are implicated in the worsening of bupivacaine cardiotoxicity or (2) how hexamethonium acts to reduce bupivacaine-induced cardiotoxicity.

The first aim of the current study was to determine whether the parasympathetic system might worsen bupivacaine cardiotoxicity. For this purpose, we compared the cardiotoxic profile of bupivacaine on the evolution of RR, PR, and HV intervals; QRS duration; and $LVdP/dt_{max}$ in pentobarbital-anesthetized dogs with and without atropine pretreatment. The second aim of this study was to verify in our model whether hexamethonium pretreatment could reduce the bupivacaine cardiotoxic profile on the parameters indicated above. Finally, to try to understand the mechanism of the putative cardioprotection of hexamethonium, we hypothesized that hexamethonium, by decreasing heart rate, might reduce the blockade of cardiac sodium channels by reducing the use-dependent block and therefore might reduce bupivacaine-induced impairment of ventricular conduction. For that purpose, we paced the right atrium of dogs pretreated with hexamethonium and then given a large dose of bupivacaine to obtain a heart rate similar to that of dogs given bupivacaine alone.

Materials and Methods

Animal Preparation

The principles for the care and treatment of experimental animals complied with the national guidelines of the French Ministry of Agriculture. We used an experimental electrophysiologic model on closed-chest dogs anesthetized with sodium pentobarbital.[18,19] Twenty-two mongrel dogs of either sex, weighing 10–15 kg, were anesthetized with sodium pentobarbital (40 mg/kg iv). The trachea was then intubated, and the lungs were mechanically ventilated with room air (74052, B. Braun, Melsungen, Germany). Body temperature was maintained at 38°C ± 0.5 with an MR 450 rewarming humidifier device (Fisher and Paykel, Auckland, New Zealand). We previously had determined that this anesthetic procedure allows good stability of electrophysiologic and hemodynamic parameters for the duration of the measurement period.[11]

The animals were instrumented as previously described.[10,11] Electrocardiographic recordings were

taken from standard lead II. A 6-French bipolar electrode catheter (USCI, C. R. Bard, Billerica, MA) was introduced *via* the femoral vein under fluoroscopy into the right ventricle, close to the interventricular septum near the tricuspid valve to record the His-bundle electrogram.[19] In ten dogs, another 6-French bipolar electrode catheter was introduced *via* the femoral vein under fluoroscopy into the right atrium for atrial pacing. Drugs were administered through a 6-French venous catheter in the contralateral femoral vein. A 5-French Teflon catheter (Plastimed, Saint-Leu La Forêt, France) was inserted into the femoral artery and advanced into the descending aorta to withdraw arterial blood samples to verify blood gases (pH > 7.35, arterial oxygen tension > 80 mmHg, and arterial carbon dioxide tension < 40 mmHg; Instrument Laboratory 1306 pH/blood gas analyzer, Milano, Italy), and to assay plasma bupivacaine concentrations. The contralateral femoral artery was cannulated with a 6-French double high-fidelity micromanometer (Millar Instruments, Houston, TX) that was advanced into the left ventricle under fluoroscopy to measure left ventricular and aortic pressures.

Experimental Protocol

Two groups of 6 dogs each and one group of 10 dogs were studied. In each animal, a 30-min period was allowed to verify the stability of the preparation. All dogs were given 4 mg/kg iv bupivacaine (bupivacaine HCl 0.5%, R. Bellon, France) over 10 s. We previously had demonstrated that this dose of bupivacaine induces marked myocardial depression and major electrophysiologic changes without causing cardiovascular collapse or immediate cardiac death.[10,11] All dogs were also given a saline solution (3.5 $ml \cdot kg^{-1} \cdot h^{-1}$ iv).

Group 1 was given only bupivacaine. In group 2, each animal was given 0.2 mg/kg iv atropine sulfate 5 min before bupivacaine administration. This dose of atropine had been demonstrated to inhibit completely the cardiac responses to stimulation of the cervical vagus nerves for 70–90 min in trials in our and others'[20] laboratories. Group 3 (n = 10) was given 10 mg/kg iv of hexamethonium and then 4 mg/kg iv bupivacaine over 10 s, 5 min after hexamethonium injection. All dogs of group 3 were also given a previous vascular loading of 25 ml/kg saline solution just before and during the administration of hexamethonium. Then the rate of the saline solution was 3.5 $ml \cdot kg^{-1} \cdot h^{-1}$ iv as reported above. Preliminary trials in our laboratory had shown the ability of this dose of hexamethonium to inhibit completely the effects of electric vagal stimulation on the sinus and atrioventricular nodes 70–90 min after hexamethonium administration. Moreover, the electrophysiologic and hemodynamic parameters were stable from 5 to 65 min after the administration of 10 mg/kg hexamethonium given alone.

Measurements

The following electrophysiologic measurements (expressed in milliseconds) were made: cardiac cycle length (RR interval); PR interval measured from the onset of the P wave to the Q wave of the QRS complex; atria–His interval (AH), measured from the onset of the atrial depolarization to the His bundle electrogram of the endocavitary lead; HV interval, measured from the His bundle electrogram of the endocavitary lead to the Q wave of electrocardiographic lead II; QRS duration; and QT interval corrected by heart rate ($QTc = QT/\sqrt{RR}$, Bazett formula). In addition, in group 3, after hexamethonium pretreatment, HV interval and QRS duration were measured during the 15 s of atrial pacing (Stimulator CSO, Savita, Paris, France) at a basic cycle length of 400 ms (150 beats/min). We chose this basic cycle length because it was the mean of the RR interval obtained in dogs given only bupivacaine (group 1). The stimulation intensity was three times the diastolic threshold, and its duration was 3 ms.

The following hemodynamic variables were measured: mean aortic pressure (millimeters mercury), left ventricular end-diastolic pressure (millimeters mercury), and $LVdP/dt_{max}$ (millimeters mercury per second) as an index of contractility[21] derived with a Gould differentiator. All of these variables were recorded on an ES 1000 polygraph (100 mm/s) (Gould, Oxnard, CA). The plasma concentration of bupivacaine was determined by high-pressure liquid chromatography.[22,23]

Electrophysiologic and hemodynamic parameters were recorded before the administration of atropine sulfate in group 2 and before the administration of hexamethonium in group 3. In all groups, these parameters were recorded just before the administration of bupivacaine (0 min, baseline) and then at 1, 2, 3, 4, 5, 10, 15, and 30 min after bupivacaine administration. Arterial blood samples for plasma bupivacaine assay were withdrawn before and at the end of bupivacaine injection and then 3, 15, and 30 min later.

Statistical Analysis

Results are expressed as means ± standard deviations. The effects of atropine and hexamethonium in groups 2 and 3 and the effects of bupivacaine in all groups

were tested using one-way analysis of variance for repeated measures followed by contrast study and completed by Bonferroni's correction. Data from groups 2 and 3 were compared to those from group 1 to test the effects of atropine and hexamethonium pretreatments, respectively, after bupivacaine administration, using two-way analysis of variance for repeated measures followed by contrast study and completed by Bonferroni's correction. Similarly, the electrophysiologic parameters measured during atrial pacing in group 3 were compared to those of group 1 using the tests indicated above, and to those of group 3 obtained at a spontaneous rate using a paired Wilcoxon's test. Values of $P < 0.05$ were considered to indicate statistical significance. All results were analyzed with a 1990 version 6 SAS computer program (SAS Institute, Cary, NC).

Results

Effects of Bupivacaine Alone

As shown in table 1, the administration of bupivacaine alone in group 1 induced significant bradycardia. Bupivacaine also markedly impaired atrioventricular conduction, lengthening the PR interval by more than 60%, the AH interval by more than 27%, and the HV interval by more than 130% ($P < 0.001$ from 1 to 15 min and $P < 0.05$ at 30 min; fig. 1). QRS duration (fig. 1) was widened by more than 100% ($P < 0.001$ from 1 to 15 min and $P < 0.05$ at 30 min). Bupivacaine also altered ventricular repolarization, with more than 40% prolongation of the QTc interval.

As reported in table 2, bupivacaine also impaired hemodynamic parameters. Mean aortic pressure was transiently decreased by 25%, and $LVdP/dt_{max}$ was significantly decreased by more than 50%, while left ventricular end-diastolic pressure significantly increased by more than 100%.

Effects of Atropine Sulfate and Hexamethonium Pretreatments

The administration of atropine in group 2 did not significantly modify electrophysiologic and hemodynamic parameters. The administration of bupivacaine in group 2 induced electrophysiologic and hemodynamic alterations similar to those in group 1 (tables 1

Table 1. Electrophysiologic Variables

Group	Before Atropine (Group 2) or Hexamethonium (Group 3)	Baseline	1 Min	2 Min	3 Min	4 Min	5 Min	10 Min	15 Min	30 Min
RR (ms)										
2	381 ± 98	372 ± 90	437 ± 114	453 ± 123*	450 ± 126*	455 ± 128*	457 ± 133*	445 ± 130*	435 ± 129	432 ± 141
1	—	355 ± 34	387 ± 30*	393 ± 28*	400 ± 25*	399 ± 23*	398 ± 23†	406 ± 58*	410 ± 71	391 ± 86
			$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.002$	$P < 0.006$
3	368 ± 69†	483 ± 68	542 ± 66‡	563 ± 74‡	568 ± 74‡	578 ± 76‡	590 ± 83‡	577 ± 81‡	574 ± 78‡	569 ± 97‡
PR (ms)										
2	97 ± 3	92 ± 8	139 ± 11†	142 ± 15†	140 ± 15†	140 ± 14†	137 ± 15†	127 ± 17*	118 ± 17	111 ± 14
1	—	87 ± 4	140 ± 4‡	142 ± 3‡	139 ± 4‡	137 ± 5‡	134 ± 6‡	120 ± 6‡	111 ± 7‡	98 ± 7*
								$P < 0.03$	$P < 0.02$	$P < 0.02$
3	89 ± 6†	102 ± 8	148 ± 16‡	153 ± 21‡	156 ± 23‡	157 ± 25‡	154 ± 26‡	145 ± 23‡	135 ± 19‡	121 ± 20†
AH (ms)										
2	60 ± 6	56 ± 6	69 ± 7	71 ± 8	71 ± 8	71 ± 8	71 ± 7	71 ± 7	70 ± 6*	66 ± 3*
1	—	54 ± 3	67 ± 4*	69 ± 2†	69 ± 2†	69 ± 2†	66 ± 2†	66 ± 4†	64 ± 5†	60 ± 6*
				$P < 0.02$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$
3	56 ± 4†	67 ± 5	78 ± 10‡	84 ± 12‡	88 ± 14‡	89 ± 15†	91 ± 16†	86 ± 15†	83 ± 13‡	79 ± 15†
QTc										
2	333 ± 16	333 ± 15	417 ± 43*	425 ± 47*	430 ± 46*	427 ± 42*	423 ± 43*	400 ± 29	378 ± 29	372 ± 25
1	—	330 ± 6	466 ± 33†	467 ± 22‡	462 ± 18‡	451 ± 17‡	444 ± 22‡	390 ± 18†	363 ± 20*	344 ± 16
			$P < 0.03$	$P < 0.005$	$P < 0.02$	$P < 0.03$	$P < 0.05$			
3	328 ± 12*	319 ± 11	411 ± 27†	406 ± 28‡	403 ± 33‡	400 ± 31‡	398 ± 32‡	378 ± 24†	354 ± 19*	333 ± 15

Data are expressed as mean ± SD.

Group 1 = bupivacaine alone; Group 2 = atropine plus bupivacaine; Group 3 = hexamethonium plus bupivacaine; RR = sinus cycle length; PR = PR interval; AH = Atria-his interval; QTc = QT interval corrected by RR interval.

Intragroup comparisons from baseline: *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$. P represents the comparison between groups 1 and 3. No differences were observed between groups 1 and 2.

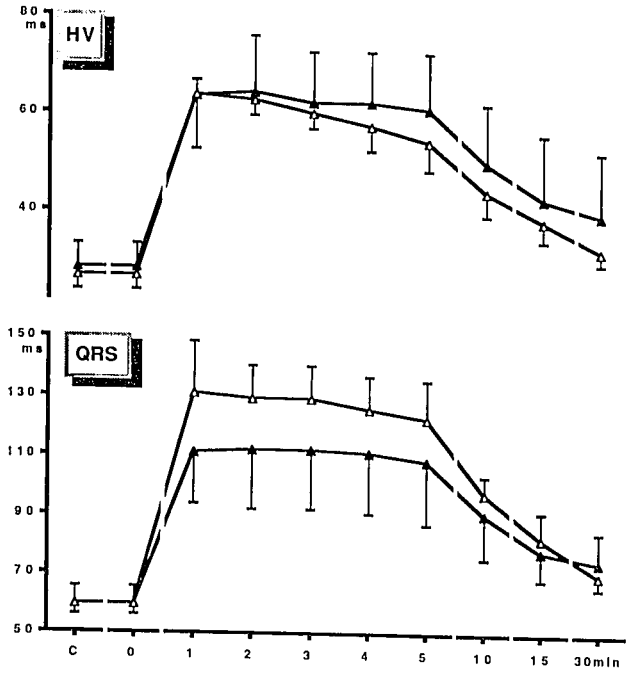

Fig. 1. Effects of bupivacaine alone (open triangles) (group 1) *versus* atropine and bupivacaine (filled triangles) (group 2) on the parameters of ventricular conduction velocities: HV interval (HV) and QRS duration (QRS). The difference between group 1 and group 2 is not significant.

and 2). Specially, the HV interval was significantly lengthened ($P < 0.001$ from 1 to 4 min, $P < 0.002$ at 5 min, and $P < 0.02$ at 10 min; fig. 1), and QRS was significantly widened ($P = 0.02$ at 1 min, $P < 0.03$ from 2 to 4 min, and $P < 0.004$ at 5 min; fig. 1). Moreover, the comparison between groups 1 and 2 shows that atropine pretreatment did not change the course of these parameters after bupivacaine administration (tables 1 and 2 and fig. 1).

Among the ten dogs of group 3, one dog died from ventricular fibrillation induced by atrial pacing 1 min after bupivacaine administration. Therefore, the results of group 3 included only nine dogs. As reported in table 1, the administration of hexamethonium before bupivacaine administration in group 3 induced significant bradycardia, PR lengthening, AH lengthening, and QTc shortening, while HV interval and QRS duration were not modified. Similarly, as indicated in table 2, the administration of hexamethonium significantly decreased mean aortic pressure and $LVdP/dt_{max}$. The administration of bupivacaine in the group given hexamethonium (group 3; tables 1 and 2) induced alterations similar to those in the group given bupivacaine

Table 2. Hemodynamic Variables

	Before Atropine (Group 2) Hexamethonium (Group 3)	Baseline	1 Min	2 Min	3 Min	4 Min	5 Min	10 Min	15 Min	30 Min
MAoP (mmHg)										
2	121 ± 28	123 ± 30	108 ± 38	105 ± 32	108 ± 29	115 ± 35	116 ± 32	113 ± 29	115 ± 31	118 ± 28
1	—	129 ± 14	97 ± 24	101 ± 26	107 ± 19	112 ± 16	118 ± 11	125 ± 11	124 ± 15	130 ± 16
			$P < 0.02$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.001$	$P < 0.01$	$P < 0.01$	$P < 0.001$
3	132 ± 17*	106 ± 16	65 ± 11‡	60 ± 12‡	59 ± 14‡	60 ± 16‡	62 ± 17‡	76 ± 23†	82 ± 20†	96 ± 14†
LVdP/dtmax (mmHg/s)										
2	1,625 ± 253	1,667 ± 325	729 ± 175†	808 ± 107†	850 ± 164†	900 ± 226*	950 ± 230†	983 ± 221*	1,050 ± 247	1,275 ± 144
1	—	1,217 ± 172	550 ± 176‡	567 ± 163‡	675 ± 181‡	742 ± 208†	800 ± 226‡	967 ± 199*	1,058 ± 203	1,242 ± 193
			$P < 0.01$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$
3	1,689 ± 287†	1,128 ± 272	450 ± 103‡	411 ± 114‡	411 ± 134‡	400 ± 125‡	411 ± 141‡	572 ± 267‡	683 ± 310‡	856 ± 290‡
LVEDP (mmHg)										
2	6 ± 5	7 ± 3	14 ± 6*	14 ± 5*	12 ± 3*	12 ± 4*	12 ± 4	10 ± 4	9 ± 4	8 ± 5
1	—	7 ± 2	13 ± 2‡	14 ± 2‡	11 ± 2†	11 ± 2†	11 ± 4	8 ± 7	8 ± 7	8 ± 6
3	5 ± 3	10 ± 4	15 ± 6†	15 ± 5†	14 ± 5†	15 ± 6†	14 ± 6†	13 ± 4*	12 ± 4	9 ± 4

Data are expressed as mean ± SD.

Group 1 = bupivacaine alone; Group 2 = atropine plus bupivacaine; Group 3 = hexamethonium plus bupivacaine; MAoP = mean aortic pressure; LVdp/dtmax = first derivative of left ventricule pressure; LVEDP = left ventricle end diastolic pressure.

Intragroup comparisons from baseline: *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$. P represens the comparison between groups 1 and 3. No differences were observed between groups 1 and 2.

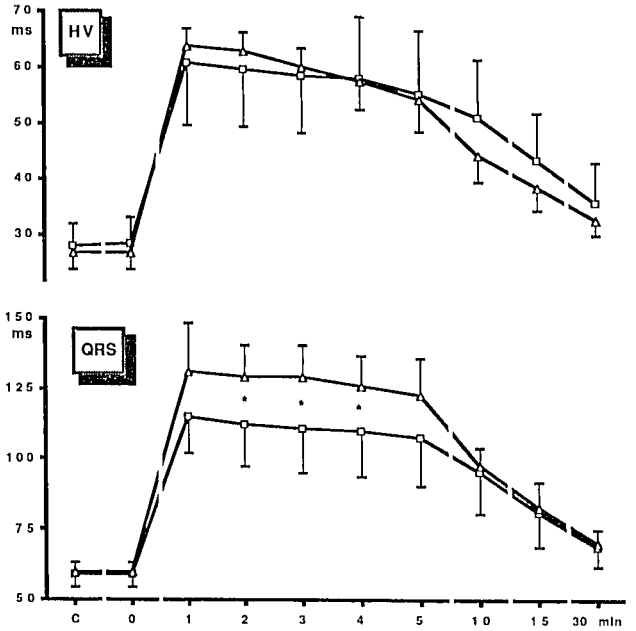

Fig. 2. Effects of bupivacaine alone (triangles) (group 1) *versus* hexamethonium and bupivacaine (squares) (group 3, n = 9) on the parameters of ventricular conduction velocities: HV interval (HV) and QRS duration (QRS). *Significance of the comparison between group 1 and group 3: $P < 0.05$. As shown in table 1, heart rate was significantly decreased in group 3.

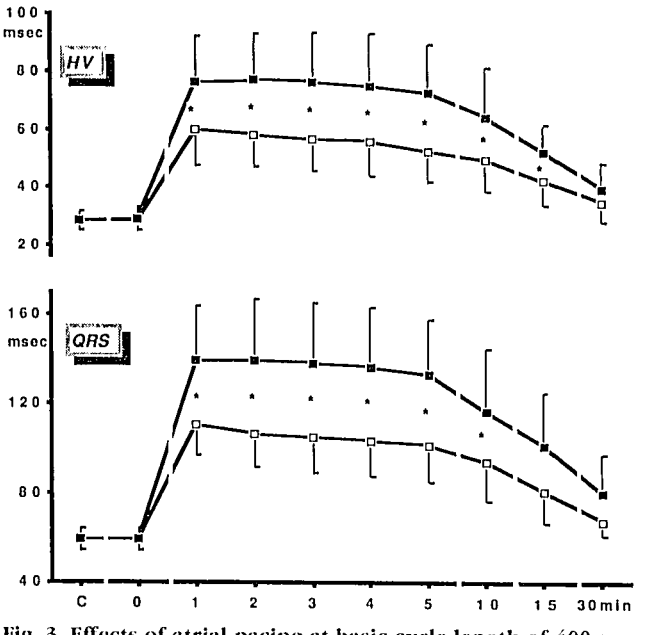

Fig. 3. Effects of atrial pacing at basic cycle length of 400 ms (filled squares) *versus* spontaneous sinus rhythm (open squares) in the six paced dogs of group 3 given hexamethonium + bupivacaine on the parameters of ventricular conduction velocities: HV interval (HV) and QRS duration (QRS). *Significance of the comparison between spontaneous rate and paced rate: $P = 0.032$.

alone (group 1). In particular, the HV interval was significantly lengthened ($P < 0.001$ from 1 to 15 min and $P < 0.005$ at 30 min; fig. 2), and QRS was significantly widened ($P < 0.001$ from 1 to 10 min and $P < 0.002$ at 15 and 30 min; fig. 2). However, the comparison between groups 1 and 3 shows that whereas hexamethonium pretreatment significantly enhanced bupivacaine-induced bradycardia and PR and AH lengthening (table 1), it nonetheless caused less widening of QRS (fig. 2) and less prolongation of the QTc interval than in group 1 (table 1). Moreover, the decrease in mean aortic pressure and in $LVdP/dt_{max}$ was significantly more pronounced in group 3 than in group 1 (table 2).

Effects of Atrial Pacing

Right atrial pacing was performed at a basic cycle length of 400 ± 5 ms. In three dogs, the atrium could not be adequately paced after bupivacaine was administered, and therefore the effects of atrial pacing were studied only in the six dogs of group 3 in whom the atrium could be paced. The spontaneous QRS of these six paced dogs was less widened than was the spontaneous QRS of all nine dogs of group 3 after bupivacaine administration (*e.g.*, 110.8 ± 13.6 *vs.* 114.4 ± 13.1 ms, respectively, at 1 min after bupivacaine administration). Figure 3 shows the evolution of the lengthening of HV interval and of the widening of QRS in the six dogs of group 3 given bupivacaine after hexamethonium pretreatment at a spontaneous rate and during atrial pacing. Atrial pacing induced significant increase in HV lengthening and QRS widening. The comparison of the course of QRS duration between groups 1 and 3 during atrial pacing was no longer significant.

Table 3. Plasma Bupivacaine Levels after Intravenous Bolus Administration

Group	Immediately after Bupivacaine Injection	3 Min	15 Min	30 Min
1	53.4 ± 15.8	7.5 ± 1.3	4.6 ± 1.0	3.2 ± 0.9
2	58.5 ± 8.3	4.9 ± 1.4	2.0 ± 0.5	1.3 ± 0.6
3	63.4 ± 9.5	6.4 ± 1.5	2.9 ± 1.0	2.1 ± 0.8

Data are expressed as mean (μg/ml) ± SD.

Group 1 = bupivacaine; Group 2 = atropine plus bupivacaine; Group 3 = hexamethonium plus bupivacaine.

Plasma Bupivacaine Concentration

Plasma bupivacaine concentrations are reported in table 3. In all dogs, bupivacaine concentrations remained in the toxic range from the end of bupivacaine iv bolus administration to 15 min later. No difference was observed between groups.

Discussion

This study shows that atropine pretreatment did not change the cardiac electrophysiologic effects induced by a large dose of bupivacaine in pentobarbital-anesthetized dogs. In contrast, hexamethonium pretreatment had opposite effects. Hexamethonium pretreatment induced less prolongation of QRS and QTc after bupivacaine administration. This evidence of improved conduction occurred despite enhanced bradycardia, lengthened PR and AH intervals, and a greater decrease in mean aortic pressure and in $LVdP/dt_{max}$. Moreover, in the group given hexamethonium, atrial pacing at a basic cycle length of 400 ms (150 beats/min) (*i.e.*, at a heart rate similar to that of the group given only bupivacaine), induced a QRS impairment similar to that of the group given only bupivacaine.

Effects of Bupivacaine

Bupivacaine in group 1 induced bradycardia, atrioventricular prolongation, QRS widening, QT lengthening, a decrease in $LVdP/dt_{max}$, and an increase in left ventricular end-diastolic pressure. These phenomena have already been reported in the literature for humans[24] and for anesthetized[9,25] and conscious animals.[26] We chose the iv bolus of 4 mg/kg bupivacaine because we observed that in previous studies[10,11,27] this dose had induced toxic plasma bupivacaine concentrations and reproducible electrophysiologic and hemodynamic impairments without causing immediate death by cardiovascular collapse or ventricular arrhythmias. In particular, QRS and HV intervals are always prolonged by more than 100%. These parameters are known to be directly correlated with ventricular conduction velocity and with His–Purkinje conduction velocity, respectively.[19,28] It is also well established that the main mechanism of ventricular arrhythmias induced by local anesthetics and other class-1b and -1c antiarrhythmic drugs is the slowing of ventricular conduction velocities, inducing a reentry phenomenon.[1,29,30] Indeed, using ventricular mapping in anesthetized dogs given incremental doses of lidocaine, Anderson *et al.*[29] demonstrated that ventricular tachycardia is induced at high plasma concentrations of lidocaine. These authors also reported that activation patterns obtained just before the onset of ventricular tachycardias simultaneously showed marked slowing of ventricular conduction velocities and QRS widening. Using ventricular epicardial mapping in rabbit hearts, we demonstrated that bupivacaine facilitates reentrant arrhythmias because bupivacaine dramatically slows ventricular conduction velocity in a dose- and use-dependent manner and induces arcs of functional conduction blocks.[8] Taking of all these findings into account, we postulate that any drug that maintains better cardiac conduction after bupivacaine administration, as demonstrated by decreased lengthening of the HV or QRS interval, should also prevent the occurrence of ventricular arrhythmias.

Effects of Atropine Sulfate or Hexamethonium Pretreatment

Atropine pretreatment did not modify any electrophysiologic or any hemodynamic parameter after bupivacaine had been administered. In previous trials, we had observed that the dose of 0.2 mg/kg atropine sulfate completely inhibited the effects of electric stimulation of the left vagus nerve on the heart for 70–90 min. Other authors have demonstrated that this dose of atropine sulfate is also able to block completely the heart response to vagal stimulation in another anesthetized dog model.[20] We can therefore postulate that the deleterious activation of the autonomic nervous system induced by bupivacaine, as proposed by Bernards and Artru,[17] is not mediated by a marked alteration of the parasympathetic system.

Hexamethonium pretreatment of dogs induced a lesser widening of the QRS and a shorter prolongation of the QTc after administration of bupivacaine than was seen in dogs given only bupivacaine. In previous trials, we had observed that the dose of 10 mg/kg hexamethonium induced stability of the electrophysiologic and hemodynamic parameters from 5 min after its administration to 65 min and completely abolished cardiac response to the electric stimulation of the left vagus nerve for 70–90 min. In our study, we showed that hexamethonium induced bradycardia, PR and AH lengthening, and QTc shortening. Because hexamethonium pretreatment induced a lesser QRS widening and QTc prolongation after bupivacaine exposure, we can postulate, as reported by Bernards and Artru,[17,31] that hexamethonium is able to decrease the risk of bupi-

vacaine-induced ventricular arrhythmias in anesthetized dogs and that the deleterious activation of the autonomic nervous system induced by bupivacaine is mediated by the activation of the sympathetic nervous system.

However, all of these proposals must be tempered by two facts. First, the beneficial effects of hexamethonium pretreatment on QRS alterations are due only to hexamethonium-enhanced bradycardia. Indeed, in our model, the atrial pacing performed in group 3 at a basic cycle length similar to that in the group given only bupivacaine worsened QRS widening to the same extent as in the group given only bupivacaine. This suggests that the deleterious effect of the activation of the sympathetic system induced by bupivacaine is due only to the higher heart rate induced by catecholamine release. Indeed, as previously described,[1,8] the higher the heart rate or the shorter the basic cycle length of pacing, the more potent the bupivacaine-induced decrease in $\dot{V}_{max}$ and slowing of ventricular conduction velocity. In a recent study, Bernards and Artru[31] confirmed the participation of the sympathetic nervous system when bupivacaine is administered by the iv route. However, these authors did not find any correlation between heart rate and the onset of arrhythmias in rabbits given toxic iv doses of bupivacaine and anesthetized with the combination of halothane and nitrous oxide. Bernards and Artru offered no specific explanation, but they speculated that the mechanism of bupivacaine-induced arrhythmias in their model was not the facilitation of reentry by the use-dependent block but rather either after-depolarization or abnormal automaticity.[31] However, no study has reported that bupivacaine induced after-depolarization or abnormal automaticity. Moreover, all class-1 antiarrhythmic drugs, such as lidocaine,[1,29] bupivacaine,[1,8,30] quinidine,[32,33] procainamide,[28] flecainide,[30,33,34] and propafenone[33] induce dose- and use-dependent block of cardiac sodium channels; this is commonly accepted and has even been demonstrated in humans. Indeed, Ranger *et al.*[33,34] showed that the QRS complex of patients given flecainide, quinidine, or propafenone widens when heart rate increases during exercise or ventricular pacing. One ventricular tachycardia even occurred in a flecainide-treated patient in whom the widening of QRS induced by the increase in heart rate was the greatest.[34] In our study, one dog died from ventricular fibrillation induced by atrial pacing. Ventricular fibrillation was preceded by four incremental and excessive QRS widenings induced by the higher atrial rate. Thus, we conclude that bupivacaine-induced ventricular arrhythmias are due to arcs of conduction blocks induced by the dose- and use-dependent slowing of ventricular conduction velocities. Finally, we postulate that the activation of the sympathetic nervous system, by inducing a higher heart rate, enhances the use-dependent block induced by bupivacaine and could therefore facilitate reentrant ventricular arrhythmias.

Second, in our model, the activation of the sympathetic nervous system does not seem to be as deleterious as suggested by Bernards and Artru.[17,31] Indeed, hexamethonium pretreatment did not modify the HV interval, enhanced bupivacaine-induced PR and AH lengthening, and particularly worsened hemodynamic parameters such as mean aortic pressure and $LVdP/dt_{max}$. On the other hand, using the same model, we previously reported that propranolol pretreatment does not significantly modify HV and QRS prolongation but worsens all other electrophysiologic parameters and especially hemodynamic parameters after administration of bupivacaine.[35] A recent case report confirmed that the combination of cardiac glycosides and of β-blocking agents worsens bupivacaine cardiotoxicity.[36] Conversely, we also reported in pentobarbital-anesthetized dogs that dobutamine infusion improves all of the hemodynamic parameters altered by bupivacaine while HV interval and QRS duration are not modified.[11] Thus, we postulate that hexamethonium pretreatment does not protect anesthetized dogs against bupivacaine cardiotoxicity and that the beneficial effect of hexamethonium on QRS duration is due only to the more potent decrease in heart rate induced by the ganglioplegic drug.

Limitations

In addition to the limitations previously described, it must be emphasized that, except for one dog in group 3, the dogs suffered neither cardiovascular collapse nor ventricular arrhythmias. Therefore, we cannot extrapolate our results on the beneficial or deleterious effect of the activation of autonomic nervous system during these events. However, dogs in group 3 had low blood pressure (about 60 mmHg). This seems to confirm the deleterious effect of autonomic blockade.

Dogs were anesthetized with sodium pentobarbital, which is known to modify the activity of the autonomic nervous system.[37] We used a large single dose of sodium pentobarbital, which might blunt the response of the autonomic nervous system. Moreover, it is well known that sodium pentobarbital decreases vagal tone and in-

creases sympathetic tone. These effects could modify autonomic nervous system–induced cardiac response after bupivacaine administration. It could therefore be argued that atropine sulfate given to dogs of group 2 caused no modifications because sodium pentobarbital had inhibited vagal tone. However, as mentioned above, in a pilot study, despite anesthesia with sodium pentobarbital, the electric stimulation of the vagus nerve induced extreme bradycardia and atrioventricular block, which were completely reversed after the iv administration of 0.2 mg/kg atropine sulfate. Thus, if bupivacaine had induced marked activation of the parasympathetic system, the comparison between groups 1 and 2 would have been significant. It could be also argued that the differences in AH, PR, QRS, QTc, and hemodynamic alterations that we observed between group 1 and group 3 are due only to sodium pentobarbital: this drug had increased sympathetic tone and therefore heart rate in group 1, whereas hexamethonium pretreatment in group 3 suppressed sympathetic tone induced by sodium pentobarbital and therefore corrected heart rate.

In fact, all of these points confirm that sympathetic tone, by increasing heart rate, enhances the slowing of ventricular conduction and could therefore facilitate the occurrence of ventricular arrhythmias. Indeed, it must be emphasized that sympathetic tone is implicated in bupivacaine cardiotoxicity. Hasselström *et al.*,[24] studying conscious humans, reported that iv infusion of bupivacaine increased plasma catecholamine concentrations. More recently, Bernards and Artru[31] confirmed in rabbits anesthetized with the combination of halothane and nitrous oxide that toxic iv doses of bupivacaine induced an activation of the sympathetic nervous system. Thus, whatever the mechanism, we can postulate that sympathetic nervous system was activated in group 1, whereas it was not activated in group 3.

Sodium pentobarbital protects against convulsions that can accentuate direct bupivacaine-induced cardiotoxicity by inducing hypoxia and acidosis.[11,38–41] Nevertheless, as we have previously reported,[11,42] sodium pentobarbital induces good stability of the electrophysiologic and hemodynamic parameters for the duration of the measurement period. This anesthetic drug is also widely used in experimental studies concerning other class-1 antiarrhythmic drugs, with reliable results. Moreover, sodium pentobarbital with or without suxamethonium had been proposed for treatment of bupivacaine-induced convulsions and for facilitation of tracheal intubation in the case of toxic accident.[43–45] Thus, the discrepancies between our study and the study of Bernards and Artru[17] might in part be explained by the difference in animal species (dogs *vs.* rabbits) and the difference in the anesthetic agent used (pentobarbital *vs.* halothane). Like sodium pentobarbital, halothane is known to modify the activity of the autonomic nervous system.[46]

Clinical Implications

This study and others[35,36,47] suggest that the inhibition of the autonomic nervous system enhances bupivacaine cardiotoxicity. Therefore, it must be emphasized that impairment of the autonomic nervous system induced by concurrent disease or by previous treatment such as by β-adrenergic blocking agents might enhance bupivacaine cardiotoxicity. Furthermore, whatever the effects of the autonomic nervous system, this study confirms *in vivo* that the increase in heart rate worsens the parameters of ventricular conduction when a large dose of bupivacaine is administered. The use-dependency of bupivacaine has been demonstrated by Clarkson and Hondeghem[1] on the $\dot{V}_{max}$ of action potentials of guinea pig papillary muscle and confirmed by other authors.[4,48] As indicated above, we also reported[8] in a Langendorff preparation that the increase in pacing rate worsens the slowing of ventricular conduction velocity in the left ventricle epicardium of the rabbit heart, facilitating reentrant ventricular arrhythmias. In the current study, when atrial pacing was performed in dogs given bupivacaine and hexamethonium, one dog died from ventricular fibrillation, and the six other dogs had greater QRS widening and HV lengthening. All of these observations suggest that, in the case of bupivacaine-induced cardiotoxicity, procedures inducing an increase in ventricular rate (*i.e.*, ventricular pacing) should be avoided as much as possible. It is difficult to find a positive inotropic agent that does not have some degree of positive chronotropic effect to treat bupivacaine-induced contractility depression.[11] Consequently, one is left balancing the attempt to improve contractility with the problem that such drugs also increase tachycardia, which will worsen conduction.

In summary, atropine pretreatment did not modify the cardiotoxic effects of bupivacaine in pentobarbital-anesthetized dogs. This suggests that the deleterious effect of the activation of the autonomic nervous system is not mediated by the parasympathetic system. Hexamethonium pretreatment worsened hemodynamic parameters, although electrophysiologic ventricular pa-

rameters were impaired to a lesser extent after administration of bupivacaine. This beneficial effect was due only to the bradycardic effect induced by hexamethonium in pentobarbital-anesthetized dogs. This suggests that the activation of the sympathetic system induced by bupivacaine in pentobarbital-anesthetized dogs is not as deleterious as that suggested in previously reported experimental models.

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