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Effects of Lidocaine on Myocardial Contractility and Baroreflex Control of Heart Rate in Conscious Dogs

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The effects of intravenous lidocaine (30 and 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during 30 min) at steady-state plasma levels (1.9 ± 0.2 and 3.5 ± 0.2 $\mu g/ml$, respectively) were investigated in conscious dogs, previously instrumented for measurements of arterial and left ventricular (LV) pressures, isometric myocardial contractility indexes (LV peak rate of tension development [dP/dt] and LV [dP/dt]/DP40), and heart rate. In addition, before and at the end of lidocaine infusions, arterial baroreflex responses were tested by bolus injections of nitroglycerin and phenylephrine. Whereas LV peak dP/dt and LV (dP/dt)/DP40 were significantly decreased after the low dosage of lidocaine, these indexes returned to control values after the 10th min of infusion of the high dosage. Moreover, eight out of 14 dogs exhibited continuous tremors, tachycardia, hypertension, and increase in contractility after the 10th min of lidocaine infusion (60 $\mu g \cdot kg^{-1} \cdot min^{-1}$), although their lidocaine plasma levels (3.7 ± 0.2 $\mu g/ml$) did not differ from those of the whole group. When these dogs were pretreated by combined alpha- and beta-adrenoceptor blocking drugs, none of them had tremors, and there was a constant depressant effect on cardiac chronotropism and inotropism. A specific enhancement of baroreflex sensitivity after phenylephrine injection was observed at the high lidocaine dosage. It is concluded that a central stimulation of both components of the autonomic nervous system modulates the direct effects of therapeutic plasma levels of lidocaine on cardiac chronotropism and inotropism in conscious dogs. (Key words: Anesthetics, local: lidocaine. Heart: contractility; rate. Reflexes: baroreflex. Sympathetic nervous system.)

MOST OF THE PREVIOUS studies that attempted to define a relationship between the administered dose of lidocaine and its cardiovascular effects were conducted in anesthetized animals. However, general anesthesia is known to modify the hepatic blood flow and, perhaps, the elimination rate of lidocaine[1,2] and to alter the response of the cardiovascular system to physiologic and pharmacologic interventions.[3] More recently, acute cardiovascular and neurologic toxicities of high, single, intravenous doses of local anesthetic drugs have been studied in awake dogs.[4,5]

Thus, the major goals of the present study were to: 1) reinvestigate the effects on cardiac chronotropism and inotropism of lidocaine at two perfusion rates, inducing stable plasma levels comparable with those observed during uncomplicated regional anesthesia or antiarrhythmic therapy in humans, and 2) study the potential alteration in baroreflex control of heart rate at these two dosages. This study was conducted in conscious and chronically implanted dogs in order to avoid the deleterious effects of general anesthesia and the trauma of acute surgical manipulation. In addition, to determine the extent to which the sympathetic component of the autonomic nervous system modulates the cardiovascular effects of lidocaine, a number of experiments were performed after prior combined alpha- and beta-adrenergic blockade.

Methods and Materials

PREPARATION

Mongrel dogs, weighing 14 to 22 kg, were anesthetized with intravenous sodium pentobarbital, 30 mg/kg. Through a left thoracotomy in the fifth intercostal space, a miniature pressure transducer (JSI 400®, Janssen Scientific Instruments, France, Noisy le Grand, 93160) was implanted through a stab wound in the apex of the left ventricle (LV). Heparin-filled Tygon® catheters were implanted in the left atrium and the descending thoracic aorta. Electrodes were sutured to the epicardial surface of both left and right ventricles and were later used to record the ECG. The leads to the cardiovascular instrumentation were tunneled subcutaneously and exteriorized in the intrascapular region.

Studies were conducted at least 3 weeks after surgery when the animals were healthy and trained to lie quietly in the conscious state. On each experimental day, the dogs breathed room air spontaneously. Arterial blood gas measurements (Pa_{O_2}, Pa_{CO_2}, pH) were made in an ABL-2® Acid-Base Laboratory (Radiometer, Copenhagen) to insure that no significant change was observed throughout the experiment. Laboratory ambient air temperature was always 19° C to 22° C. Arterial and left atrial pressures were recorded from the implanted, fluid-filled catheters connected to Statham P23Db® strain gauge manometers (Statham Instruments Inc, Oxnard, CA). LV systolic and end-diastolic pressures were measured from the implanted

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JSI 400® pressure transducer, which was calibrated *in vitro* against a mercury manometer and *in vivo* at the end of each experiment. Zero adjustment *in vivo* was performed using the left atrial pressure zero as a reference after matching the "a wave" of the left atrial pressure tracing with the "a wave" of the LV pressure wave form. Continuous records of dP/dt were derived from the LV pressure signal using an electronic differentiator. The ratio of dP/dt to a common isovolumic developed pressure of 40 mmHg (LV [dP/dt]/DP40) was measured by averaging over five beats.[6] A cardiotachometer triggered by ECG provided continuous and instantaneous records of heart rate. Data were recorded on a multichannel electrostatic recorder (ES 1000®, Gould Inc, Instruments Division, Cleveland, OH).

Protocols

Two groups of dogs were studied. In the first group (n = 7), a 18-gauge indwelling catheter was positioned in a hindlimb vein for the intravenous (iv) injection of drugs 15 min before the study. After an iv bolus dose of lidocaine hydrochloride (1.5 mg/kg), a 50-min iv infusion of lidocaine was administered at either 30 or 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Both dosages were administered in random sequence to each animal at 1-week intervals. Arterial blood samples were collected at 1, 5, 10, 15, 30, and 50 min of infusion to assay lidocaine plasma levels in duplicate by enzyme immunoassay (EMIT®; EMIT-cad®, lidocaine assay, Syva, Palo Alto, California).[7] Hemodynamic measurements were performed before the lidocaine iv bolus and at the same times the blood samples were drawn until 30 min. To determine whether lidocaine interferes with the baroreflex control of heart rate, baroreflex testing was performed, adapted from Billman *et al.*,[8] before the iv bolus and between the 30th and 50th min of lidocaine infusion.

Intravenous bolus injections of nitroglycerin (10 μg/kg) and phenylephrine (5 μg/kg) in a volume of 1 ml were given in random sequence to decrease or increase, respectively, systolic arterial pressure by 20–30 mmHg. Each injection was followed by a control period of 10–15 min to allow heart rate and blood pressure to return to their preinjection values. Each R–R interval was plotted as a function of the preceding systolic pressure. The analysis was performed beat-by-beat, beginning only after the first noticeable change in R–R interval. Basal values were obtained by averaging over five successive beats immediately before the vasoactive drug infusion. Baroreflex sensitivity was expressed as the slope of the regression line between systolic blood pressure and R–R interval. The slope was accepted for further analysis if the correlation coefficient was 0.80 or greater.

In the second group, seven other conscious dogs received lidocaine, 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and the hemodynamic responses were recorded in the same conditions as in the previous group. However, in order to determine the extent to which the sympathetic component of the autonomic nervous system modulates the cardiovascular effects of lidocaine at this dosage, these dogs were also studied after prior blockade of beta-adrenoceptors (propranolol, 2 mg/kg) and combined alpha 1- and alpha 2-adrenoceptors (phentolamine, 1 mg/kg, followed by an infusion of 1 mg/min). The adequacy of beta-adrenoceptor blockade was shown by the absence of chronotropic response to isoproterenol, 0.1 μg/kg, and that of alpha-adrenoceptor blockade by the absence of pressor response to norepinephrine, 0.2 μg/kg. Adrenergic blockade was tested before and after the lidocaine infusion.

Treatment of Data

Average values ± standard errors of the mean (SEM) are reported. All data were compared by analysis of variance (ANOVA) for repeated measures followed by Neuman Keul's multiple-range test.

Results

Plasma Levels and Hemodynamic Effects of Lidocaine in Intact Dogs (table 1)

Lidocaine, 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Steady-state plasma levels of lidocaine were achieved as early as after 5 min of infusion. Between 1 and 5 min, mean arterial and LV systolic pressures, LV peak dP/dt and LV (dP/dt)/DP40 were decreased without concomitant changes in heart rate and LV end-diastolic pressure. However, after 30 min, only LV (dP/dt)/DP40 remained significantly decreased as compared with the control value.

Lidocaine, 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Since plasma levels, control values, and general pattern of hemodynamic variables in intact dogs receiving lidocaine, 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$, in the two groups were almost identical, all these values were pooled. Steady-state plasma levels of lidocaine were also achieved at this dosage, and at any time from 5 min, these plasma levels were significantly higher with lidocaine, 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$, than with lidocaine, 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.001$). Mean arterial pressure, LV peak pressures, and LV (dP/dt)/DP40 were decreased after 5 min of lidocaine infusion without changes in heart rate, LV end-diastolic pressure, and LV dP/dt. However, in contrast with the lidocaine infusion dosage, 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$, all the hemodynamic variables returned near or even above their prelidocaine infusion values after the 15th min of lidocaine infusion.

TABLE 1. Comparison of Hemodynamic Changes Induced by the Two Dosages of Lidocaine Infusion (L 30 = 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and L 60 = 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in Conscious Dogs

	n	Pre-lidocaine Infusion Values	Lidocaine Infusion Time (min)				
			1	5	10	15	30
Lidocaine plasma levels ($\mu g/ml$)							
L 30	7	—	3.5 ± 0.6	2.3 ± 0.1	1.9 ± 0.1	2.0 ± 0.3	1.9 ± 0.2
L 60	14	—	5.1 ± 0.4	3.6 ± 0.1	3.4 ± 0.1	3.5 ± 0.1	3.6 ± 0.2
Heart rate (beats/min)							
L 30	7	82 ± 7	84 ± 7	81 ± 7	82 ± 6	89 ± 5	95 ± 6
L 60	14	88 ± 2	91 ± 2	85 ± 2	89 ± 3	89 ± 4	96 ± 4
Mean arterial pressure (mmHg)							
L 30	7	101 ± 4	95 ± 2*	95 ± 3*	96 ± 3	97 ± 4	98 ± 3
L 60	14	95 ± 2	92 ± 2	90 ± 1*	94 ± 2	95 ± 2	101 ± 3
LV peak pressure (mmHg)							
L 30	6	135 ± 3	125 ± 4*	125 ± 4*	128 ± 5	130 ± 4	129 ± 5
L 60	14	132 ± 2	128 ± 2	126 ± 2*	130 ± 2	134 ± 2	143 ± 4*
LV end-diastolic pressure (mmHg)							
L 30	6	5.3 ± 0.7	5.6 ± 0.3	6.8 ± 0.3	6.3 ± 0.5	6.0 ± 0.5	5.5 ± 0.6
L 60	14	6.1 ± 0.4	6.6 ± 0.5	6.0 ± 0.5	5.9 ± 0.4	6.0 ± 0.3	5.6 ± 0.3
LV peak dP/dt (mmHg/s)							
L 30	6	3171 ± 211	2767 ± 209*	2820 ± 286*	2879 ± 188*	3159 ± 265	3204 ± 344
L 60	14	3060 ± 65	2806 ± 89*	2876 ± 97	2976 ± 83	3049 ± 121	3259 ± 129
LV (dP/dt)/DP 40 (s − 1)							
L 30	6	65.1 ± 4.4	54.2 ± 3.3*	52.2 ± 3.7*	53.8 ± 3.3*	54.6 ± 3.6*	55.0 ± 3.6*
L 60	14	61.4 ± 2.7	53.6 ± 2.2*	53.8 ± 1.4*	54.3 ± 2.5	55.8 ± 1.7	58.0 ± 1.7

LV = left ventricular; dP/dt = maximum rate of tension development; DP = developed pressure.

Values are means ± SEM.

* Significant changes from prelidocaine infusion values: $P < 0.05$.

EFFECTS OF LIDOCAINE ON REFLEX CONTROL OF HEART RATE (FIG. 1)

Lidocaine, 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Changes in R–R interval induced by phenylephrine and nitroglycerin bolus injections were similar before and after 30 min of lidocaine infusion. Moreover, baroreflex sensitivities during activation (phenylephrine) and deactivation (nitroglycerin) were virtually identical before and after lidocaine infusion (respectively, 20.7 ± 3.3 *vs.* 22.7 ± 1.8 and 12.4 ± 1.5 *vs.* 13.8 ± 1.9 ms/mmHg).

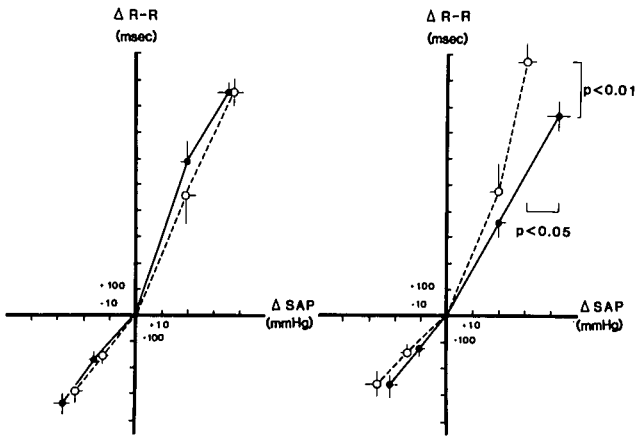

FIG. 1. Baroreflex-induced changes in R–R interval (ΔR–R) resulting from phenylephrine-induced increases in systolic arterial pressure (ΔSAP) and nitroglycerin-induced decreases in systolic arterial pressure before (—— ●) and after (--- ○) the 30th min of lidocaine infusion at 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (left side) and 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (right side). Change from control of R–R interval was obtained near midpoint of pressure rise and at peak rise in systolic arterial pressure.

Lidocaine, 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Despite a reduced phenylephrine-induced hypertension, the resulting R–R interval lengthening was increased during lidocaine infusion at this dosage. Thus, the baroreflex sensitivity during activation was enhanced from 21.8 ± 3.6 to 25.8 ± 3.6 ms/mmHg ($P < 0.01$). The baroreflex-induced change in R–R interval resulting from nitroglycerin-induced decrease in systolic arterial pressure and the baroreflex sensitivity during deactivation were unchanged (11.3 ± 1.9 *vs.* 11.8 ± 1.5 ms/mmHg).

INFLUENCE OF TREMORS ON HEMODYNAMIC EFFECTS DURING LIDOCAINE INFUSION, 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$, IN INTACT DOGS (TABLE 2)

When lidocaine was infused at this dosage, eight out of 14 dogs (four out of seven in group 1 and four out of seven in group 2) exhibited continuous tremors after the 10th min of lidocaine infusion, although the lidocaine plasma levels were in the same range for all dogs. The appearance of tremors was concomitant with a significant increase in heart rate (without arrhythmia), mean arterial and LV peak pressures, LV peak dP/dt, and LV (dP/

TABLE 2. Influence of Tremors on Hemodynamic Changes during Lidocaine Infusion (60 $\mu g \cdot kg^{-1} \cdot min^{-1}$)

	n	Prelidocaine Infusion Values	Lidocaine Infusion Time (min)				
			1	5	10	15	30
Lidocaine plasma levels (μg/ml)							
without tremors	6	—	4.8 ± 0.5	3.6 ± 0.1	3.6 ± 0.2	3.5 ± 0.1	3.6 ± 0.1
with tremors	8	—	5.4 ± 0.6	3.6 ± 0.2	3.3 ± 0.1	3.5 ± 0.2	3.5 ± 0.4
Heart rate (beats/min)							
without tremors	6	89 ± 3	92 ± 5	88 ± 5	90 ± 6	88 ± 6	87 ± 5
with tremors	8	88 ± 2	91 ± 2	83 ± 2	88 ± 4	93 ± 4*†	104 ± 6*†
Mean arterial pressure (mmHg)							
without tremors	6	94 ± 2	93 ± 2	88 ± 3	92 ± 4	90 ± 4	92 ± 5
with tremors	8	92 ± 1	90 ± 2	88 ± 1	93 ± 3	96 ± 1†	104 ± 4*†
LV peak pressure (mmHg)							
without tremors	6	136 ± 2	129 ± 3	128 ± 4	130 ± 4	130 ± 4	137 ± 7
with tremors	8	128 ± 3	126 ± 2	125 ± 3	131 ± 3	137 ± 3*†	149 ± 4*†
LV end-diastolic pressure (mmHg)							
without tremors	6	6.4 ± 0.6	6.9 ± 0.6	6.0 ± 0.4	5.9 ± 0.3	6.2 ± 0.4	5.6 ± 0.3
with tremors	8	5.8 ± 0.6	6.4 ± 0.8	6.1 ± 0.8	6.0 ± 0.7	5.8 ± 0.5	5.7 ± 0.6
LV peak dP/dt (mmHg/s)							
without tremors	6	3090 ± 90	2799 ± 77*	2887 ± 106*	2893 ± 121*	2957 ± 110*	2960 ± 151*
with tremors	8	3037 ± 96	2811 ± 147	2852 ± 155	2990 ± 126	3166 ± 188*†	3446 ± 148*†
LV (dP/dt)/DP 40 (s − 1)							
without tremors	6	64.2 ± 3.5	56.6 ± 3.2*	56.9 ± 3.7*	51.5 ± 2.8*	54.0 ± 3.2*	54.1 ± 2.4*
with tremors	8	59.2 ± 3.3	51.3 ± 2.9*	52.5 ± 2.8*	55.6 ± 3.0*	58.8 ± 3.0†	62.7 ± 3.2*†

See table 1 for abbreviations.
Values are means ± SEM.
* Significant changes from prelidocaine infusion values: $p < 0.05$.
† Significant changes between tremoring and nontremoring dogs: $P < 0.05$.

dt)/DP40 as compared with prelidocaine infusion values and to corresponding values in nontremoring dogs.

INFLUENCE OF PRIOR ADRENOCEPTOR BLOCKADE ON HEMODYNAMIC EFFECTS OF LIDOCAINE, 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (TABLE 3)

In the second experimental group, pretreatment with alpha- and beta-adrenoceptor-blocking drugs resulted in significantly greater lidocaine plasma levels. None of the animals exhibited tremors, but five out of seven showed salivation. Lidocaine induced a progressive and significant decrease in heart rate, mean arterial and LV peak pressures, LV peak dP/dt, and LV (dP/dt)/DP40 as compared with prelidocaine infusion values under adrenoceptor blockade and with corresponding values in the same intact dogs after the 10th min of lidocaine infusion.

Discussion

The present investigation, conducted in intact unanesthetized dogs instrumented for direct and continuous measurement of cardiac rate and contractility, clearly demonstrates that the increase in lidocaine dosage does not enhance the depression of myocardial performance. These data are in contrast with those previously reported either in *in vitro*¶ or in *in vivo* preparations under general anesthesia.[9] These differences can probably be attributed to central and/or reflex cardiovascular adjustments through the autonomic nervous system that modulate the direct myocardial depressant effect of lidocaine.

The two dosages of lidocaine, 30 and 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$ after an iv bolus, were selected in order to: 1) allow convenient administration in conscious dogs, and 2) achieve steady-state lidocaine plasma levels with a time course almost similar to that observed in humans when this local anesthetic drug is used either for regional anesthesia[10] or intravenously for its antiarrhythmic properties.[11] Complete adrenoceptor blockade in our study increases arterial lidocaine concentrations to the same extent as in a previous work,[12] which was conducted under general anesthesia and beta-adrenoceptor blockade alone. In such conditions, the increase in lidocaine plasma levels was reported to be related to a considerable reduction in cardiac output and hepatic blood flow. A possible influence of propranolol on hepatic drug-metabolizing capacity was also discussed.[13]

¶ Block A, Covino BG: Effects of local anesthetic agents on cardiac conduction and contractility. Regional Anesthesia 6:55–61, 1981

TABLE 3. Influence of Combined Alpha- and Beta-adrenoceptor Blockade on Hemodynamic Changes during Lidocaine Infusion (60 $\mu g \cdot kg^{-1} \cdot min^{-1}$)

	n	Pre-lidocaine Infusion Values	Lidocaine Infusion Time (min)				
			1	5	10	15	30
Lidocaine plasma levels (μg/ml)							
intact dogs	7	—	5.5 ± 0.5	3.7 ± 0.2	3.6 ± 0.2	3.4 ± 0.1	3.8 ± 0.4
adrenergic blocked dogs	7	—	6.9 ± 0.6†	4.8 ± 0.2†	4.9 ± 0.2†	4.8 ± 0.1†	5.2 ± 0.2†
Heart rate (beats/min)							
intact dogs	7	90 ± 1	91 ± 2	86 ± 1	93 ± 2	94 ± 2	96 ± 4
adrenergic blocked dogs	7	94 ± 3	88 ± 3	86 ± 2*	88 ± 5	85 ± 3	83 ± 3*
Mean arterial pressure (mmHg)							
intact dogs	7	96 ± 2	95 ± 2	90 ± 2*	98 ± 2	98 ± 2	105 ± 4*
adrenergic blocked dogs	7	90 ± 2	86 ± 3	87 ± 2*	87 ± 2*	86 ± 2*†	84 ± 2*†
LV peak pressure (mmHg)							
intact dogs	7	132 ± 4	131 ± 2	128 ± 4	135 ± 3	137 ± 3	147 ± 4*
adrenergic blocked dogs	7	118 ± 4	110 ± 3*	109 ± 3*	111 ± 4*	106 ± 3*†	103 ± 3*†
LV end-diastolic pressure (mmHg)							
intact dogs	7	5.1 ± 0.4	5.1 ± 0.4	4.8 ± 0.3	5.2 ± 0.4	5.2 ± 0.4	5.0 ± 0.3
Adrenergic blocked dogs	7	4.3 ± 0.5	4.6 ± 0.5	4.1 ± 0.6	4.0 ± 0.4	3.9 ± 0.3	3.8 ± 0.4
LV peak dP/dt (mmHg/s)							
intact dogs	7	3000 ± 69	2760 ± 70*	2804 ± 100*	2949 ± 66	2971 ± 111	3170 ± 131*
adrenergic blocked dogs	7	2517 ± 68	2190 ± 77*	2305 ± 73*	2217 ± 54*	2186 ± 6*†	2153 ± 58*†
LV (dP/dt)/DP 40 (s − 1)							
intact dogs	7	61.9 ± 3.7	54.0 ± 2.7*	51.6 ± 2.1*	53.8 ± 3.3*	55.2 ± 3.8	57.2 ± 3.8
adrenergic blocked dogs	7	50.8 ± 1.6	45.1 ± 1.2*	45.1 ± 1.2*	45.4 ± 1.2*	44.1 ± 1.4*†	44.9 ± 1.2*†

See table 1 for abbreviations.
Values are means ± SEM.
* Significant changes from pre-lidocaine infusion values: $P < 0.05$.
† Significant changes between intact and adrenergic blocked dogs: $P < 0.05$.

At the low dosage, 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$, lidocaine decreased the myocardial contractility, probably in relation to its well-known intrinsic negative inotropic effect.[14] This was reflected by the sustained decrease in LV (dP/dt)/DP40, which is a useful indirect index of myocardial inotropism because it is almost insensitive to changes in preload and afterload.[15,16] Surprisingly, by increasing the lidocaine dosage, the depressant effect on myocardial contractility was no longer significant, as reflected by no major changes in both LV peak dP/dt and LV (dP/dt)/DP40 after the 10th min of lidocaine infusion, 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$. This lack of negative inotropic effects for the whole group cannot be attributed to a concomitant tachycardia by itself because the increase in heart rate for the whole group at this lidocaine dosage was not significant and because it has clearly been demonstrated that the Bowditch phenomenon exerts little influence on cardiac inotropism in the intact conscious dog over the physiologic range of heart-rate values.[17] The absence of depression in heart rate, mean arterial pressure, and LV systolic pressure when the rate of infused lidocaine was doubled, or even their increase in the case of tremoring dogs, suggests that a reflex increase in sympathetic tone occurs. Our data confirm this hypothesis because, after combined pretreatment with alpha- and beta-adrenoceptor blocking drugs, all cardiovascular variables are then depressed by lidocaine. Several arguments from the present experiments suggest that this sympathetic stimulation is of central origin since: 1) the time-course analysis of these cardiovascular adjustments shows that they are not instantaneous in contrast to rapid reflexes originating from peripheral receptors because they appeared progressively between 5 and 30 min of lidocaine infusion, and 2) these adjustments were not of similar magnitude in all dogs because those exhibiting tremors developed greater increases in heart rate, mean arterial pressure, LV peak dP/dt, and LV (dP/dt)/DP40 than the nontremoring dogs.

There are some speculative arguments from the present study suggesting that parasympathetic tone is increased simultaneously with the sympathetic tone during lidocaine infusion, 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Thus, there is: 1) an increase in baroreflex sensitivity after phenylephrine bolus injection, a phenomenon exclusively related to an enhancement of cardiac vagal tone when this technique is used to investigate the baroreflex control of heart rate,[18,19] 2) a progressive decrease in heart rate in dogs with alpha- and beta-adrenoceptors blockade, which may be attributed to an increase in vagal restraint, although a direct effect on the sinus node cannot be totally excluded,[20] and 3) an abundant salivation after the 10th min of lidocaine in-

fusion in these dogs. Such parasympathetic stimulation might be of central origin, too, but it must be kept in mind that an enhancement of adrenergic vasoconstrictor tone on barosensitive areas modulates by itself the baroreceptor input and, thus, increases the resulting activity of the parasympathetic efferent pathway.[21,22] Finally, the unexpected lack of alteration in baroreflex sensitivity after nitroglycerin injection, despite the concomitant increase in sympathetic tone, may be related to the fact that examination of the initial slope of the R–R interval as a function of arterial pressure changes exaggerates the importance of the parasympathetic responses, which are evoked more rapidly than the sympathetic ones.[23,24]

In conclusion, it seems clear that a central stimulation of both components of the autonomic nervous system modulates the direct effects of therapeutic plasma levels of lidocaine on cardiac chronotropism and inotropism in conscious dogs. This could explain the weak overall cardiotoxicity of this local anesthetic, especially during the management of many cardiac arrhythmias. Moreover, the increases in sympathetic tone and vagal restraint could be linked to the premonitory signs of neurotoxicity (tremors, salivation). Because associated drugs or administration routes (especially subarachnoid and epidural injections) are known to affect deeply the baseline state of cardiac function and its integrative reflex responses, and because the present results with lidocaine might be different with other local anesthetic agents, this study suggests that the overall effects of such agents on cardiac chronotropism and inotropism need to be further reevaluated in dogs and, ultimately, in human patients.

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