J Anesth (1997) 11:38–43

Journal of
Anesthesia

Effects of bupivacaine and lidocaine on cardiac function in awake and pentobarbital-anesthetized rats

SATOSHI KASHIMOTO[1], MARIE-FRANÇOISE DOURSOUT[2], PATRICK WOUTERS[3], TAKESHI OGUCHI[1], and JACQUES E. CHELLY[2]

[1] Department of Anesthesiology, Yamanashi Medical University, 1110 Shimokato, Nakakoma-gun, Yamanashi 409-38, Japan
[2] Department of Anesthesiology, University of Texas Medical School at Houston, 6431 Fannin, 5.020MSMB, Houston, TX 77030, USA
[3] Department of Anesthesiology, Universitaire Ziekenhuizen Gasthuisberg, Leuven Catholic University, Herestraat 49, Leuven, Belgium

Abstract: Using an implanted Doppler crystal, we evaluated hemodynamic changes induced by subconvulsive doses of bupivacaine and lidocaine in awake and pentobarbital-anesthetized rats. Low doses of lidocaine ($2.0\,mg \cdot kg^{-1}$) and bupivacaine ($0.5\,mg \cdot kg^{-1}$) changed hemodynamics minimally. However, a high dose of lidocaine ($8.0\,mg \cdot kg^{-1}$) reduced heart rate, cardiac output, and regional myocardial wall thickening for a short period with or without anesthesia. In contrast, a high dose of bupivacaine ($2.0\,mg \cdot kg^{-1}$) increased mean arterial pressure and did not change heart rate or regional myocardial wall thickening in the awake state. Under pentobarbital anesthesia, a high dose of lidocaine reduced mean arterial pressure significantly shortly after the injection, but bupivacaine did not. Thus, it is unlikely that bupivacaine has more potent cardiotoxicity than lidocaine in subconvulsive doses.

Key words: Local anesthetics, Bupivacaine, Lidocaine, Heart, Cardiac function

Introduction

In 1979, Albright suggested that bupivacaine and etidocaine are selectively more cardiodepressant than agents such as lidocaine [1]. This report has led to a considerable amount of animal experimentation in an effort to clarify the mechanisms by which bupivacaine may cause cardiodepression, ventricular arrhythmias, cardiac arrest, and death. Some investigators have reported that the degree of cardiovascular depression is related to anesthetic potency [2–4], while others have suggested that bupivacaine has a greater cardiovascular toxicity and a smaller margin of safety [5–9]. This discrepancy remains to be investigated.

Address correspondence to: S. Kashimoto
Received for publication on February 2, 1996; accepted on May 24, 1996

Many studies have been performed to determine the circulatory changes caused by local anesthetics. However, acute preparation of the animal appears to interfere with the circulatory response. To avoid the negative effects of basal anesthesia and surgical stress, we recently developed a long-term instrumented rat model for the study of cardiovascular functions in the intact animal [10]. Moreover, subconvulsive doses of bupivacaine and lidocaine were used to minimize central nervous system (CNS) effects because the direct effects of local anesthetics on the heart are obscured by sympathetic activation due to the CNS effects of these drugs [11].

This study was designed to evaluate the hemodynamic changes induced by subconvulsive doses of bupivacaine and lidocaine in awake and anesthetized rats, with a special focus on myocardial contractility in vivo. Regional myocardial contraction was measured with an implanted Doppler crystal. No other study has directly compared these anesthetics in the same rat on separate days. This method can reduce variability between animals.

Methods

Experimental preparation

This study was approved by the Baylor College of Medicine Animal Protocol Review Committee. Details of the basic model have been published [10]. Briefly, eight rats (weight 290–370g) were anesthetized with halothane. Following tracheal intubation, the rats were ventilated with a small animal respirator with 30% oxygen and 1.6% halothane. After a parasternal thoracotomy, a 20-MHz pulsed Doppler flow probe (size 2.6–3.0mm) was positioned around the ascending aorta for measurement of cardiac output [12]. In addition, an epicardial Doppler crystal was sutured to the

left ventricle for measurement of the wall thickening fraction [13,14]. An 18-gauge catheter was introduced into the thoracic cavity to function as a thoracic drain until closure of the thorax. A Tygon catheter (PE-50) was inserted via a femoral artery into the abdominal aorta for recording of arterial blood pressure. Another catheter was inserted into an internal jugular vein for drug administration. All wires and catheters were threaded subcutaneously to the back of the neck where they were secured in place. After surgery, the animals were housed in individual cages to avoid damage to the implanted instruments. The animals were allowed to recover for more than 1 week and, for the first 5 postoperative days, they received gentamycin 5 mg·kg^{-1}. The catheters were flushed with heparinized saline and filled with concentrated sucrose every 3 days to prevent clot formation.

Experimental protocol

Studies began no less than 7 days after surgery. The rats were studied randomly on two occasions separated by an interval of 2 days. In the awake condition, the rats were kept in their cages during the experiment with cages covered by a cloth to avoid undue disturbance. In the awake state, a lower dose of bupivacaine (0.5 mg·kg^{-1}) or lidocaine (2.0 mg·kg^{-1}) was administered intravenously. Hemodynamic variables including mean arterial blood pressure (MAP), heart rate (HR), cardiac output (CO), and percent thickening fraction (%TF) were recorded before, 15 s, 30 s, 5 min, 10 min, 20 min, and 30 min after local anesthetic injection. A higher dose of bupivacaine (2.0 mg·kg^{-1}) or lidocaine (8.0 mg·kg^{-1}) was then given. Hemodynamic variables were also recorded 15 s, 30 s, 5 min, 10 min, 20 min, and 30 min after high-dose administration. More than 30 min later, the rats were anesthetized with intravenous pentobarbital (30 mg·kg^{-1}). The same local anesthetic was used and the same procedure followed under pentobarbital anesthesia. A half dose of pentobarbital was added if necessary. Arterial Po_2, Pco_2, and pH were measured in the awake state and 30 min after the higher dose of local anesthetic injection.

Throughout the experiments, all rats spontaneously breathed room air, and body temperature in the anesthetized rats was maintained at 37°C with a heating lamp if necessary. At the end of the experiments the animals were allowed to recover.

Blood gas measurements were performed with a standard blood gas analyzer (pH/blood gas analyzer 713, Instrumentation Laboratory, Lexington, MA, USA). Blood pressure was transduced (MP-20D, Micron Medical, Los Angeles, CA, USA) from the femoral catheter. CO and wall thickening wires were connected to the 20-MHz ultrasonic flow/dimension system. Calibration of the Doppler microprobes was described in a previous study [10]. The physiologic variables were recorded by a brush polygraph (Model-2800, Gould Electronics, Cleveland, OH, USA). The percent thickening fraction (%TF) was calculated using the following formula: $\%TF = 100 \times (SE/R)$, where SE is the systolic excursion through the range gate and R is the range-gate depth [13]. Theoretical and animal experimental validations have established the measurement of ventricular thickening fraction as an index of regional myocardial contractility [14].

Data analysis

Data were analyzed using analysis of variance (ANOVA) with repeated measures and the modified Bonferroni tests of Student's *t*-test for paired comparison. In addition, ANOVA and the Neuman-Keuls test were used for comparisons of four different conditions. Statistical significance was accepted when $P < 0.05$. Data are presented as mean ± SD.

Results

Incidence of convulsion, arrhythmia, or death

One of eight rats died after the lidocaine experiment (before the bupivacaine study). Therefore, the number of experiments with bupivacaine was 7 and that with lidocaine, 8. In the awake state, 3 of 8 rats and 1 of 7 rats had very slight convulsions (but soon recovered spontaneously) after high-dose lidocaine and bupivacaine injections, respectively. However, none of the rats had cardiac arrhythmias such as sinus arrest, arterioventricular (AV) block, or QRS widening.

Table 1. Blood gas analysis

	Before	Bupivacaine	Lidocaine
pH			
Awake	7.37 ± 0.04	7.40 ± 0.01	7.41 ± 0.02
Pentobarbital	7.39 ± 0.03	7.33 ± 0.05*,**	7.36 ± 0.04*
Pao_2(mmHg)			
Awake	90.0 ± 5.3	96.2 ± 4.6	96.4 ± 5.1
Pentobarbital	86.0 ± 6.4	89.0 ± 11.7	89.0 ± 8.2
$Paco_2$(mmHg)			
Awake	35.6 ± 3.7	32.6 ± 1.6	33.1 ± 2.3
Pentobarbital	37.5 ± 2.9	40.8 ± 3.8*	41.4 ± 4.1*
Base excess (mmol/l)			
Awake	−3.8 ± 0.7	−3.4 ± 1.2	−2.2 ± 1.7
Pentobarbital	−1.8 ± 1.6	−4.1 ± 1.8	−2.2 ± 2.2

Mean ± SD.
*$P < 0.05$ vs awake state; **$P < 0.05$ vs before.

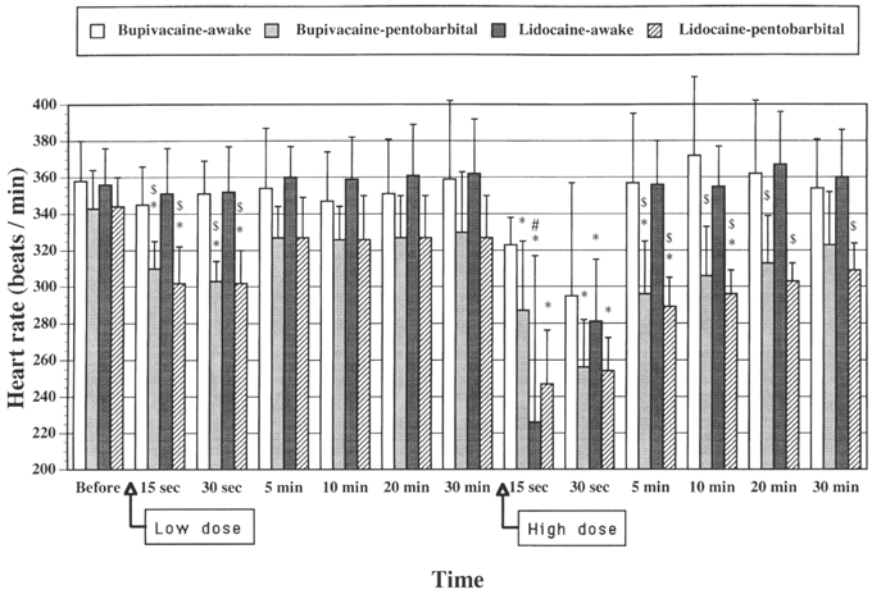

Fig. 1. Heart rate changes. Bupivacaine: $n = 7$; lidocaine: $n = 8$. $^{*}P < 0.05$ *vs* before drug injection. $^{\$}P < 0.05$ *vs* awake state. $^{\#}P < 0.05$ *vs* bupivacaine

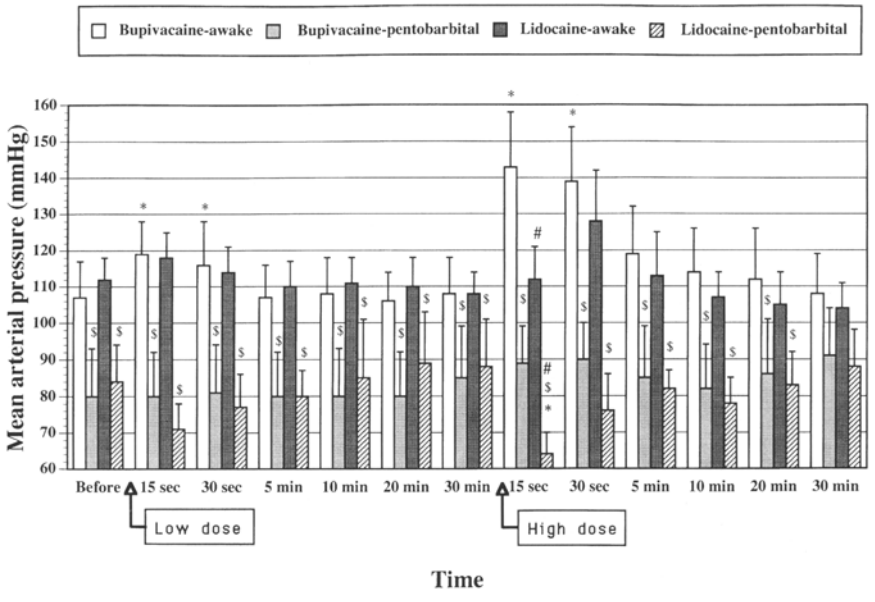

Fig. 2. Mean arterial pressure changes. Bupivacaine: $n = 7$; lidocaine: $n = 8$. $^{*}P < 0.05$ *vs* before drug injection. $^{\$}P < 0.05$ *vs* awake state. $^{\#}P < 0.05$ *vs* bupivacaine

Blood gas analysis

There were no significant differences in Pao_2 and base excess before and after drug administration with or without anesthesia. However, there were significant differences in pH and $Paco_2$ between the awake state and pentobarbital anesthesia after drug injection (Table 1).

Hemodynamic changes in the awake state

Although low doses of bupivacaine or lidocaine did not change HR significantly, a high dose of lidocaine decreased HR only immediately after administration. In addition, high-dose lidocaine reduced HR more significantly than did bupivacaine 15 s after injection (Fig. 1). Both doses of bupivacaine increased MAP shortly after injection but lidocaine did not do so significantly (Fig. 2). CO was reduced significantly by high doses of both drugs, but recovered soon (Fig. 3). Although low doses of local anesthetics did not change %TF significantly, a high dose of lidocaine decreased %TF for a short period (Fig. 4).

Hemodynamic changes under pentobarbital anesthesia

In anesthetized rats, low doses of bupivacaine and lidocaine significantly decreased HR very shortly after the injection and high doses of both drugs did so signifi-

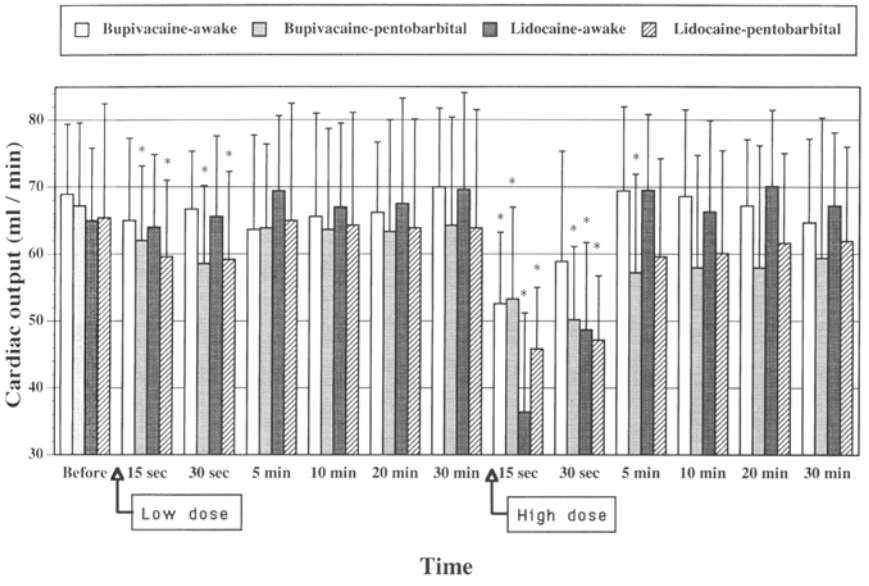

Fig. 3. Cardiac output changes. Bupivacaine: $n = 7$; lidocaine: $n = 8$. $^*P < 0.05$ *vs* before drug injection

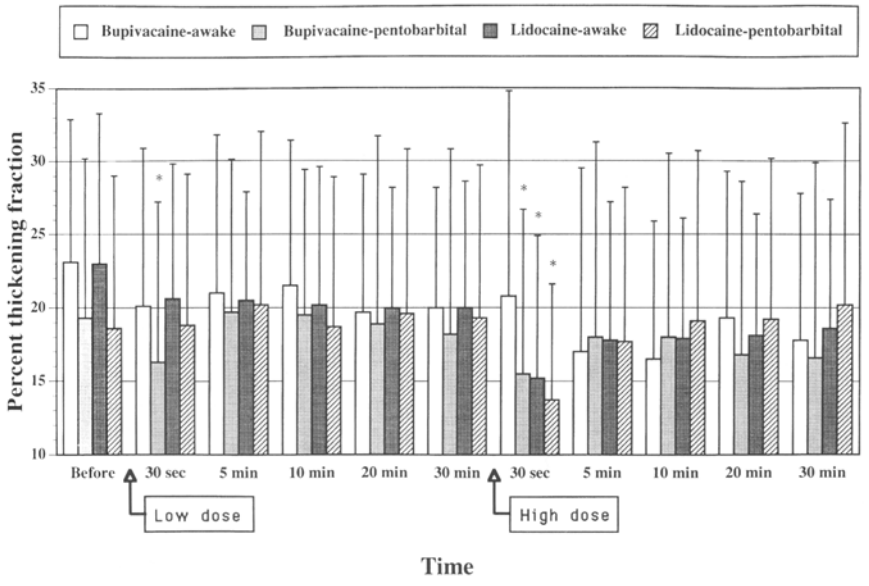

Fig. 4. Percent thickening fraction. Bupivacaine: $n = 7$; lidocaine: $n = 8$. $^*P < 0.05$ *vs* before drug injection

cantly for 5 min (Fig. 1). High doses of lidocaine significantly decreased MAP shortly after the injection (Fig. 2). High doses of two drugs reduced CO significantly; however, CO recovered soon (Fig. 3). %TF was significantly reduced for a short period with both doses of bupivacaine and a high dose of lidocaine (Fig. 4).

Differences between awake and pentobarbital anesthesia

HR in rats receiving pentobarbital was decreased significantly after both doses of local anesthetics (Fig. 1). MAP in both groups was reduced significantly with pentobarbital during the experiment (Fig. 2). However, there were no significant differences in CO and %TF between the awake state and pentobarbital anesthesia (Figure 3, 4).

Discussion

In the present study, we administered single intravenous doses of each agent separately to simulate the clinical situation of inadvertent intravascular injection and used subconvulsive doses to minimize the CNS effects since seizures affect the cardiovascular system prominently [15]. However, 3 rats had slight convulsions with lidocaine, as did 1 rat with bupivacaine in this study. The rat's threshold of convulsion may be lower

than that of other animals. For example, Chadwick [11] has reported that the mean convulsive doses were 11.7 ± 4.6 mg·kg^{-1} lidocaine and 3.8 ± 1.0 mg·kg^{-1} bupivacaine in cats. Even at low concentrations, local anesthetics depress inhibitory pathways in the CNS and cause mild sympathetic activation [16]. Therefore, the effects of local anesthetics on the heart are difficult to determine when the agents are administered intravenously in vivo.

The findings of this study indicate that there were a few differences in hemodynamic changes between equianalgesic doses of bupivacaine and lidocaine or between awake and anesthetized rats. Low doses of lidocaine (2.0 mg·kg^{-1}) and bupivacaine (0.5 mg·kg^{-1}) changed hemodynamics minimally. However, a high dose of lidocaine (8.0 mg·kg^{-1}) reduced HR, CO, and regional myocardial wall thickening for a short period with or without anesthesia, In contrast, a high dose of bupivacaine (2.0 mg·kg^{-1}) increased MAP and did not change HR or regional myocardial wall thickening in the awake state. Under pentobarbital anesthesia, a high dose of lidocaine decreased MAP significantly 15 s after the injection but bupivacaine did not. These results seem interesting because bupivacaine was not more cardiotoxic than lidocaine.

It has been reported that the cardiovascular toxicity of bupivacaine is either comparable to its anesthetic potency [2–4,11] or stronger than that of lidocaine [5–9]. In the isolated rat heart, Komai and Rusy demonstrated that the ratio between bupivacaine and lidocaine for slowing ventricular rate to 50% of control was 14:1 [5]. Tanz et al. [6] concluded that 3 μg·ml^{-1} of unbound bupivacaine was more cardiotoxic than 30 μg·ml^{-1} of unbound lidocaine in the isolated guinea pig heart. Lynch [9] found a 10:1 (lidocaine: bupivacaine) ratio for equal contractile depression in isolated papillary muscles from guinea pigs. In the isolated canine heart, the equal depression of contraction ratio was 8.1:1 (lidocaine:bupivacaine) [17]. In an in vivo study, Rosen et al. [8] demonstrated that bupivacaine was more cardiotoxic than lidocaine, and that in sheep this toxicity was enhanced by the prior presence of hypercarbia, acidosis, and hypoxia. Nancarrow et al. [18] have also reported the greater cardiotoxicity of bupivacaine compared to lidocaine in the sheep. These report support the evidence that the cardiovascular toxicity of bupivacaine is stronger than that of lidocaine.

In contrast, Nath et al. [2] studied anesthetized pigs and found the drugs to exert a dose-dependent depression of the left ventricle in the same ratio as their anesthetic potency (bupivacaine:lidocaine = 4:1), although comparable prolongations of the QRS interval with bupivacaine and lidocaine were obtained at a dose ratio of 1:16. Recent studies have also reported that the degrees of cardiotoxicity of local anesthetics are related to their anesthetic potencies [3,4].

These differences may result from several reasons. First, bupivacaine is more likely to cause sodium channel block [7], AV conduction block [5,19], and ventricular arrhythmias [11,17,20,21], and to provide easier access to the myocardial cell [22] than is lidocaine. Secondly, cardiotoxicity may be attributed to differences in species. For example, Kasten and Martin [23] have demonstrated that sheep are more sensitive to bupivacaine than are dogs. In contrast, bupivacaine given intraperitoneally is less toxic than lidocaine in mice [24]. Thirdly, it may result from the use of nonblood perfusion medium in the isolated preparations, although Cronau et al. [25] have reported that in the working rat heart model the acute depressant effects of bupivacaine and lidocaine on the cardiac function were exerted in a potency ratio of approximately 4.59, which is nearly anesthetic potency. Finally, it has been suggested that the CNS is the primary target organ for the toxic effects of local anesthetics [26], and the CNS plays a role in mediation of the cardiovascular system toxicity of local anesthetics [27]. Heavner [21] has provided evidence that actions of bupivacaine, but not lidocaine, on the CNS of cats can induce ventricular arrhythmias independent of direct cardiac effects when injected into the cerebral ventricle. However, Kotelko et al. [20] have indicated that equivalent doses of lidocaine or bupivacaine produced similar CNS toxicity when rapidly injected intravenously in conscious sheep. In our study, bupivacaine was not more cardiotoxic than lidocaine. This result may be related to the differences in species used, anesthetic doses, in vivo or in vitro studies, and experimental design.

When comparing studies of local anesthetic agents administered intravenously to intact animals, there seem to be differences related to whether or not the animal has been under general anesthesia. In the present study, under pentobarbital anesthesia the baseline of MAP was lower and high-dose lidocaine decreased MAP, but bupivacaine did not, shortly after administration. This finding is partially consistent with the report that bupivacaine has a lesser hypotensive effect than lidocaine in lightly anesthetized cats [11]. Moreover, pentobarbital anesthesia avoided the convulsions, decreased HR and pH, and increased $Paco_2$ under both conditions. These CNS effects and respiratory changes induced by anesthesia may have affected the cardiac response to local anesthetics.

In summary, there was no evidence that the margin of safety would be smaller after inadvertent intravascular administration of bupivacaine than an equianesthetic dose of lidocaine. Within the limits of extrapolation from rats to humans, it is unlikely that bupivacaine

has more potent cardiotoxicity than lidocaine in subconvulsive doses.

References

1. Albright GA (1979) Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 51:285–287
2. Nath S, Haggmark S, Johansson G, Reiz S (1986) Differential depressant and electrophysiologic cardiotoxicity of local anesthetics: An experimental study with special reference to lidocaine and bupivacaine. Anesth Analg 65:1263–1270
3. Mets B, Janicki PK, James MF, Erskine R, Sasman B (1992) Lidocaine and bupivacaine cardiorespiratory toxicity is additive: A study in rats. Anesth Analg 75:611–614
4. Fujita Y (1994) Comparative direct effects of lidocaine and bupivacaine on regional myocardial function in dogs at noncardiovascular toxic levels. Anesth Analg 78:1158–1163
5. Komai H, Rusy BF (1981) Effects of bupivacaine and lidocaine on AV conduction in the isolated rat heart: Modification by hyperkalemia. Anesthesiology 55:281–285
6. Tanz RD, Heskett T, Loehning RW, Fairfax CA (1984) Comparative cardiotoxicity of bupivacaine and lidocaine in the isolated perfused mammalian heart. Anesth Analg 63:549–556
7. Clarkson CW, Hondeghem LM (1985) Mechanism for bupivacaine depression of cardiac conduction: Fast block of sodium channels during the action potential with slow recovery from block during diastole. Anesthesiology 62:396–405
8. Rosen MA, Thigpen JW, Shnider SM, Foutz SE, Levinson G, Koike M (1985) Bupivacaine-induced cardiotoxicity in hypoxic and acidotic sheep. Anesth Analg 64:1089–1096
9. Lynch III C (1986) Depression of myocardial contractility in vitro by bupivacaine, etidocaine, and lidocaine. Anesth Analg 65:551–559
10. Kashimoto S, Doursout MF, Hartley C, Chelly JE (1993) Effects of thiopental and ketamine on cardiac function during moderate hemorrhage in chronically instrumented rats. J Cardiovasc Pharmacol 21:829–833
11. Chadwick HS (1985) Toxicity and resuscitation in lidocaine or bupivacaine-infused cats. Anesthesiology 63:385–390
12. Hartley CJ, Cole JS (1974) An ultrasonic pulsed Doppler system for measuring blood flow in small vessels. J Appl Physiol 37:626–629
13. Hartley CJ, Latson LA, Michael LH, Seidel CL, Lewis RM, Entman ML (1983) Doppler measurement of myocardial thickening with a single epicardial transducer. Am J Physiol 245:H1066–1072
14. Zhu WX, Myers ML, Hartley CJ, Roberts R, Bolli R (1986) Validation of a single crystal for measurement of transmural and epicardial thickening. Am J Physiol 251:H1045–1055
15. Selvin BL (1987) Electroconvulsive therapy—1987. Anesthesiology 67:367–385
16. Blair MR (1975) Cardiovascular pharmacology of local anaesthetics. Br J Anaesth 47:247–252
17. Wheeler DM, Bradley EL, Woods WT (1988) The electrophysiologic actions of lidocaine and bupivacaine in the isolated, perfused canine heart. Anesthesiology 68:201–212
18. Nancarrow C, Rutten AJ, Runciman WB, Mather LE, Carapetis RJ, McLean CF, Hipkins SF (1989) Myocardial and cerebral drug concentrations and the mechanisms of death after fatal intravenous doses of lidocaine, bupivacaine, and ropivacaine in the sheep. Anesth Analg 69:276–283
19. Moller RA, Convino BG (1988) Cardiac electrophysiologic effects of lidocaine and bupivacaine. Anesth Analg 67:107–114
20. Kotelko DM, Shnider SM, Dailey PA, Brizgys RV, Levinson G, Shapiro WA, Koike M, Rosen MA (1984) Bupivacaine-induced cardiac arrhythmias in sheep. Anesthesiology 60:10–18
21. Heavner JE (1986) Cardiac dysrhythmias induced by infusion of local anesthetics into the lateral cerebral ventricle of cats. Anesth Analg 65:133–138
22. de La Coussaye JE, Bassoul B, Albat B, Peray PA, Gagnol JP, Eledjam JJ, Sassine A (1992) Experimental evidence in favor of the role of intracellular actions of bupivacaine in myocardial depression. Anesth Analg 74:698–702
23. Kasten GW, Martin ST (1986) Comparison of resuscitation of sheep and dogs after bupivacaine-induced cardiovascular collapse. Anesth Analg 65:1029–1032
24. de Jong RH, Bonin JD (1980) Deaths from local anesthetic-induced convulsions in mice. Anesth Analg 59:401–405
25. Cronau LH, Merin RG, Abouleish E, Steenberg M, Melgarejo AB (1988) Functional and metabolic effects of bupivacaine and lidocaine in the perfused working rat heart. Anesth Analg 67:929–935
26. Liu PL, Feldman HS, Giasi R, Patterson MK, Covino BG (1983) Comparative CNS toxicity of lidocaine, etidocaine, bupivacaine, and tetracaine in awake dogs following rapid intravenous administration. Anesth Analg 62:375–359
27. Thomas RD, Behbehani MM, Coyle DE, Denson DD (1986) Cardiovascular toxicity of local anesthetics: An alternative hypothesis. Anesth Analg 65:444–450