

The Magnitude and Duration of Direct Myocardial Depression Following Intracoronary Local Anesthetics: A Comparison of Lidocaine and Bupivacaine

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Direct myocardial depression plays a role in the cardiovascular toxicity of local anesthetic agents, but this role is obscured by concomitant cardiac, systemic, and CNS events: seizures, hypoxia, acidosis, sympathetic activation, bradycardia, and A-V heart block. Direct injection of small bolus doses of lidocaine and bupivacaine into a branch of the left coronary artery was used to minimize these systemic effects. Regional contraction in the zone supplied by the coronary artery was measured with a sonomicrometer. Both agents caused a dose-dependent reduction in the extent of systolic contraction, and a 4.9:1 (lidocaine:bupivacaine) dose ratio produced a 50% depression of contraction. The duration of depression, taken as the time for 95% recovery of systolic contraction, was about 25% ($P < 0.05$) longer with bupivacaine for an equal degree of depression. Coronary blood flow was reduced modestly by both agents. These results suggest that differences in the magnitude or duration of direct myocardial depression cannot explain the clinical perception that the cardiovascular toxicity of bupivacaine is greater than that of lidocaine. (Key words: Anesthetics, local: bupivacaine; cardiovascular toxicity; lidocaine. Heart: blood flow, contractility.)

CARDIOVASCULAR COLLAPSE has occurred following inadvertent intravascular injection of local anesthetics during regional anesthetic procedures.¹⁻³ The clinical impression is that the severity and duration of collapse following bupivacaine is greater than that following an equi-anesthetic dose of lidocaine.¹ Hypotension and bradycardia occur following injection of both agents,⁴⁻⁶ whereas A-V heart block and ventricular arrhythmias appear to be more frequent following bupivacaine.⁷⁻¹⁰ Direct depression of myocardial contractility appears to play a role in these events, but the direct effects of local anesthetics on the heart are obscured by sympathetic activation caused by the CNS effects of the drugs.⁶ Studies in isolated hearts suggest that direct depression occurs and that, at equi-anesthetic concentrations, bupivacaine is approximately 2-3 times more potent than lidocaine in depressing myocardial contraction.^{11,12} Such evidence supports the notion that the margin of safety of bupivacaine is smaller than that of lidocaine. In contrast, a recent study in pigs that used intracoronary injections of agents to circumvent systemic effects has found that bupivacaine

and lidocaine depress blood pressure and left ventricular dP/dt in proportion to their local anesthetic potencies and thus should have similar toxic:therapeutic ratios.⁹ Because these studies provide conflicting answers, the relative magnitude of cardiac depression caused by lidocaine and bupivacaine remains controversial.

A pertinent question involves the duration of myocardial depression caused by these local anesthetic agents. The higher lipid solubility and stronger protein binding of bupivacaine compared to lidocaine suggests that the heart might extract and retain more bupivacaine, prolonging the depression. A heart:blood concentration ratio of 3.5 for bupivacaine and about 2.0 for lidocaine was found at the time of death in a recent sheep study.¹³ Markedly prolonged myocardial depression was reported by Wegrzynowicz following exposure of isolated rabbit hearts to bupivacaine but not lidocaine.¹⁴

The aim of this study was to determine the magnitude and duration of direct myocardial depression caused by intracoronary injection of lidocaine and bupivacaine. Small doses of these agents were used to minimize systemic and CNS effects. Regional myocardial contraction was measured with implanted piezoelectric crystals and a sonomicrometer. Blood pressure and heart rate were held constant to obviate the direct effects of these variables on regional contraction. Coronary blood flow was measured to determine if alterations in perfusion might account for differences in the duration of depression.

Methods

GENERAL PREPARATION

Six mongrel dogs were studied. The study was approved by the animal care and use committee. Approximately 1 h after sedation with morphine sulfate (2.5 mg/kg sc), each dog was anesthetized with an initial injection of alpha-chloralose (100 mg/kg iv). Anesthesia was maintained with a continuous infusion of alpha-chloralose (10 mg · kg⁻¹ · h⁻¹ iv) during the experiment.¹⁵ Following tracheal intubation the dogs' lungs were ventilated with oxygen with a positive-pressure pump (Harvard) operating with a 10 cmH₂O end-expiratory back pressure (Boehringer). End-expiratory carbon dioxide was monitored continuously with an infrared device (Beckman LB-1®)

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and was maintained between 4.5% and 5% by adjustment of rate of ventilation and tidal volume. Metabolic acidosis caused by chloralose anesthesia was prevented by infusion of 150 mM sodium bicarbonate, $5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ iv. Arterial blood was sampled periodically, and pH, P_{CO_2} , and P_{O_2} were determined (Instrumentation Laboratory, 813). Arterial hemoglobin concentration was determined by use of a Co-oximeter® (Instrumentation Laboratory, 282). Rectal temperature was maintained at 37° C with a heating pad and temperature controller (Yellow Springs, 73A). Blood coagulation in the extracorporeal circuit was prevented by infusion of sodium heparin (750 U/kg iv bolus plus 250 U · kg⁻¹ · h⁻¹ iv).

Arterial blood pressure was measured *via* a catheter introduced into the arch of aorta *via* the left brachial artery. A solid-state catheter-tip transducer (Millar®) was used to measure left ventricular pressure. The first derivative of left ventricular pressure with respect to time was derived with an analog circuit (Honeywell Accudata 132).

SURGICAL PREPARATION

Halothane 1.0–1.5% (inspired) was administered during a thoracotomy for placement of piezoelectric crystals in the heart and for creation of a complete A-V heart block. The left chest was entered through the fifth intercostal space, and the heart was suspended in a pericardial cradle. Formalin was injected into the region of the A-V node to produce a complete block of A-V conduction.¹⁶ A pacemaker lead was sutured to the right ventricle, and the heart was paced at a constant rate (100 beats/min). A lensed, 5 MHz piezoelectric crystal was tunneled tangentially down to the subendocardium in the area supplied by the circumflex coronary artery, and a second crystal was sutured to the epicardium at the location that minimized the distance between crystals. The location of the inner crystal and perpendicular orientation of each set was confirmed at autopsy.

Following insertion of the crystals, the pericardium was closed and the chest was closed in layers. Air in the pleural space was removed with a tube connected to an underwater seal. The lungs were reexpanded by temporary application of positive airway pressure, and halothane was discontinued. At least 45 min elapsed prior to intracoronary injection of local anesthetic.

CORONARY BLOOD FLOW MEASUREMENTS

A stainless steel cannula¹⁷ was advanced into the root of the aorta *via* the right carotid artery. The tip of this cannula was wedged into the left circumflex coronary artery. Arterial blood from a femoral artery was supplied to this cannula by an external, passive perfusion circuit.

Coronary pressure was measured at the cannula tip *via* a small internal stainless steel tube. The seal at the tip was tested by a 10-s period of stopped flow; coronary pressure fell below 20 mmHg if the seal was complete. Total flow into the circumflex coronary artery was measured with an electromagnetic flowmeter (Zepeda SWF-3RD®) located in the extracorporeal circuit. Flow per gram was calculated by dividing total flow by total weight of the perfused area. This area was defined by injection of 3–4 ml of India ink into the cannula at the end of the experiment. The weight of these areas ranged from 45 to 64 g (average 55 ± 3 , mean \pm SEM). The flowmeter was calibrated with the dog's blood by timed collection after each experiment.

LOCAL ANESTHETICS

Preservative-free bupivacaine (0.5%; Winthrop-Breon) and lidocaine (2%; Abbott) were used in the experiment. Intracoronary injection of equal volumes of saline, the vehicle used to dissolve these agents, produced no alteration in coronary flow or regional myocardial function. The local anesthetics were injected into the tubing that supplied blood to the circumflex coronary artery over a 10-s period.

EXPERIMENTAL PROTOCOL

Heart rate was controlled at 100 beats/min by ventricular pacing (Medtronic®). Arterial blood pressure was controlled at 80 mmHg by use of a pressurized blood reservoir connected to a femoral artery. This device withdrew arterial blood from the animal if arterial blood pressure was above chamber pressure. Blood was infused if vice versa.

Bolus doses of local anesthetics were injected directly into the tubing that supplied blood to the circumflex coronary artery. The type of local anesthetic and the dose were varied in a random fashion in each experiment. The order differed between animals. Sufficient time was allowed for regional contraction to return to 95–100% of the pre-injection value after each injection.

DATA ANALYSIS

The distance between the implanted crystals was measured with a sonomicrometer (Triton). This distance and hemodynamic data were recorded on an oscillograph (Gould 260®) and an FM tape recorder (Sanborn). Paper speeds of 125 mm/min were used except for short periods of 25 mm/s just before and every 20 s following injection. These faster speeds allowed accurate timing of the start and end of systole. The beginning of systole was taken as the time when LV dP/dt first left the baseline before

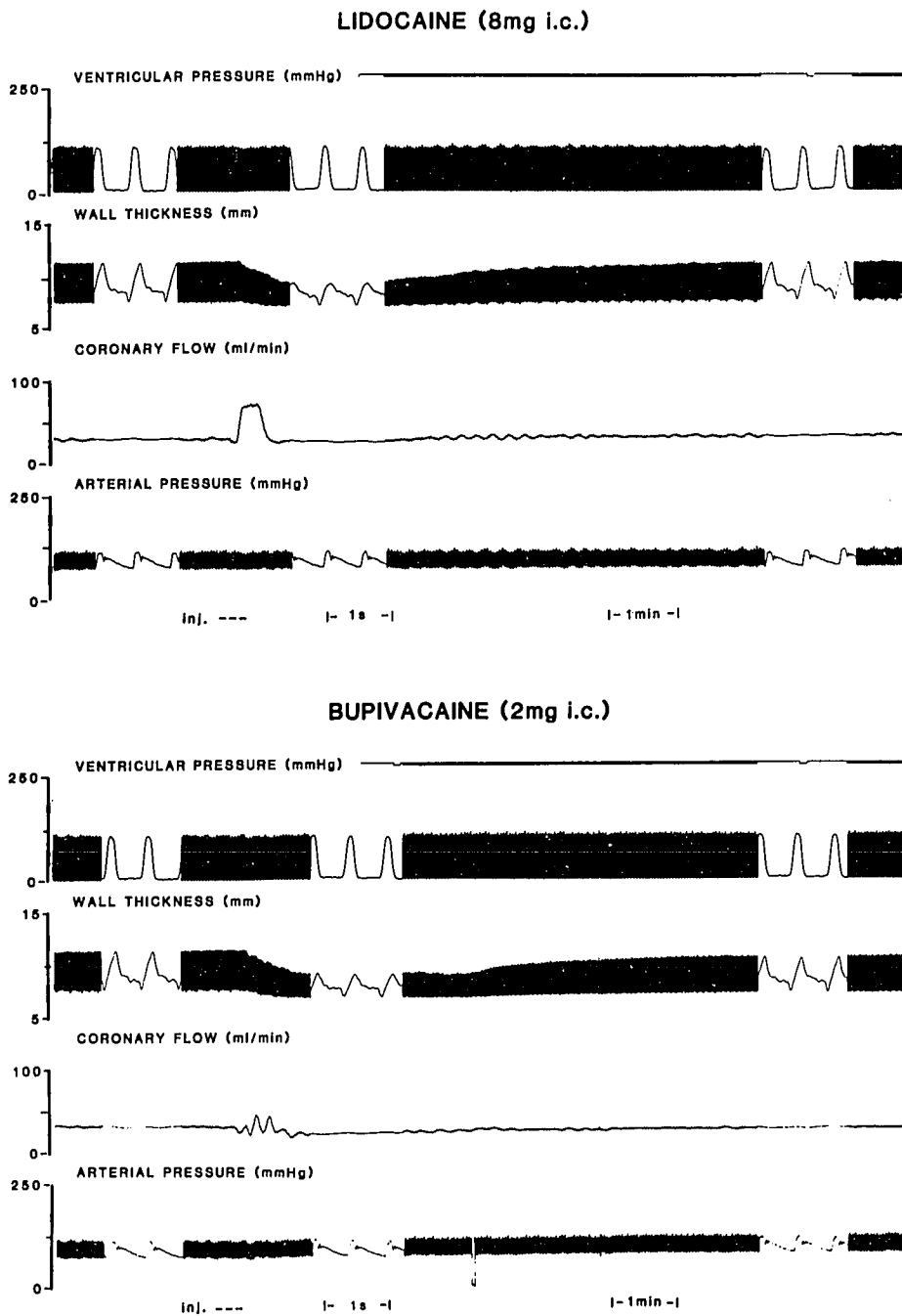


FIG. 1. Wall thickening during systole decreased following injection of lidocaine, 8 mg (top panel) or bupivacaine, 2 mg (lower panel) into the coronary artery supplying that region of myocardium. The injection occurred over a 10-s period during the period indicated by dashes in the figure's time line. A nadir in systolic contraction was reached 30–40 s following injection, and contraction gradually returned to normal levels. Blood pressure and heart rate (not shown) were unchanged in part because only about 30% of the left ventricular myocardium was exposed to the local anesthetic agent. Injection of lidocaine produced a transient increase in coronary flow; less marked changes were seen following bupivacaine. Except for these transient alterations, flow changed in parallel with regional contraction. The similarity of response between lidocaine and bupivacaine, when administered in a 4:1 ratio, is apparent. The data are from one animal.

peak-positive LV dP/dt . The end of systolic was assumed to occur 20 ms before peak-negative LV dP/dt . Values for 4–6 beats of end-systolic thickness (EST) and end-diastolic thickness (EDT) were averaged and percent thickening computed as $[(EST-EDT)/EDT] \times 100$. Systolic and diastolic arterial pressure was averaged over 6–8 beats. Mean arterial blood pressure was obtained by

electronic averaging. Heart rate was obtained from a cardiometer triggered from left ventricular pressure.

For purposes of the analysis, data were recorded approximately 20 s before intracoronary local anesthetic injection and 40 s following injection when systolic wall thickening had reached a nadir (fig. 1). The bolus injection caused transient increases in coronary blood flow, but flow

had decreased to its minimum value by 40 s. The duration of the response was taken as the time from injection to 95% recovery. This time was determined by visual inspection of the oscillograph trace.

Values for systolic thickening obtained at the nadir were divided by values obtained just prior to injection and expressed as a percent. These nadir values were plotted versus anesthetic dose on semilogarithmic paper, and the dose that produced a 50% decrease in systolic thickening was obtained for each drug in each animal by interpolation. The ratio of these interpolated values for lidocaine:bupivacaine was calculated in each animal and an average obtained over the six experimental animals.

A plot of the duration of depression versus the nadir systolic thickening values was constructed to compare the duration of the response at equivalent degrees of myocardial depression. Multivariable regression analysis using a "dummy variable" (SPSS, Version M, Release date: 1982) was used to determine if the relationships between duration and the degree of depression depended on the identity of the local anesthetic. $P < 0.05$ was considered statistically significant.

Results

Figure 1 shows the time course of events following the intracoronary injection of 8 mg lidocaine or 2 mg bupivacaine. Systolic contraction decreased following injection of both agents, reached a nadir value by 30–40 s, and slowly recovered to control. The similarity of response to equi-anesthetic doses of the two agents is apparent. Coronary flow increased transiently following lidocaine injection and then declined in parallel with regional function. A similar pattern was observed following bupivacaine except that the initial flow increase was less marked.

When values of systolic thickening at the nadir were plotted against the dose of intracoronary local anesthetic (fig. 2), roughly parallel curves were obtained for lidocaine and bupivacaine. Approximately four times as many milligrams of lidocaine as bupivacaine was required to depress systolic contraction to an equal degree over the range of 20–60% reduction from control. The interpolated values at 50% reduction (see "Methods") averaged 12.2 ± 4.9 mg (mean \pm SEM) for lidocaine and 2.5 ± 0.4 mg for bupivacaine. The ratio of these interpolated values averaged over six animals was 4.9 ± 1.7 . This result suggests that direct myocardial depression caused by each agent is comparable to its anesthetic potency.

Figure 3 shows the duration of depression versus the dose of individual agents. Depression of systolic thickening lasted longer with increasing doses of each local anesthetic. Approximately four times as much lidocaine as bupiva-

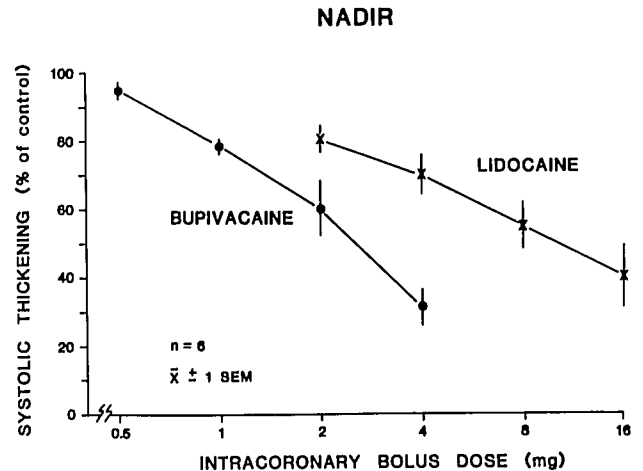


FIG. 2. Systolic thickening, expressed as a percent of the value obtained just prior to injection, is plotted versus the dose of agent, plotted on a log scale. The values shown occurred at the nadir of systolic thickening, 40 s following injection. The responses for bupivacaine and lidocaine indicate that approximately 4 times as much lidocaine was necessary to produce the same degree of depression. The values shown are means \pm 1 SEM from six dogs.

caine produced the same duration of depression. This presentation of the duration data is somewhat misleading, however, because the drugs produced different degrees of depression at equi-anesthetic doses. To compare the duration of depression at identical degrees of depression, figure 4 was constructed. This figure is a plot of the duration of depression versus systolic thickening value observed at the nadir. Multivariable regression analysis in

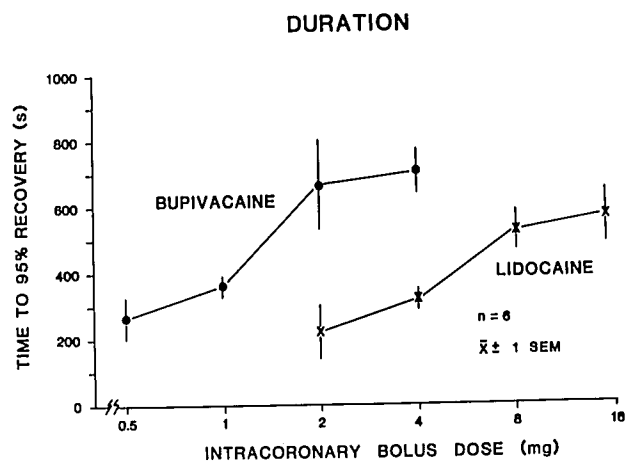


FIG. 3. The duration of myocardial depression, taken as the time required for systolic contraction to return to 95% of the pre-injection control value is shown versus the dose of agent, plotted on a log scale. The data are means \pm 1 SEM from six dogs.

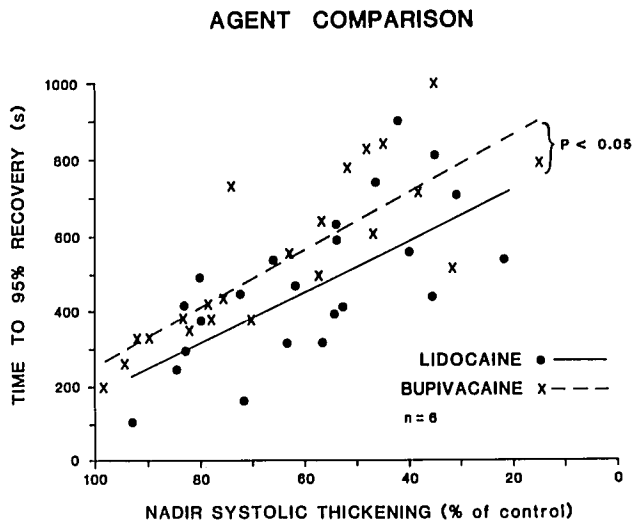


FIG. 4. The duration of myocardial depression is plotted versus the magnitude of depression observed at the nadir for both lidocaine (filled circles, solid line) and bupivacaine (crosses, dashed line). Regression analysis revealed a statistically significant ($P < 0.05$) increase in duration of about 25% for bupivacaine at all levels of depression. Data from six dogs are shown.

which the identity of the anesthetic was entered as an independent variable determined that the relationship between duration and systolic thickening did depend on the anesthetic: duration was prolonged approximately

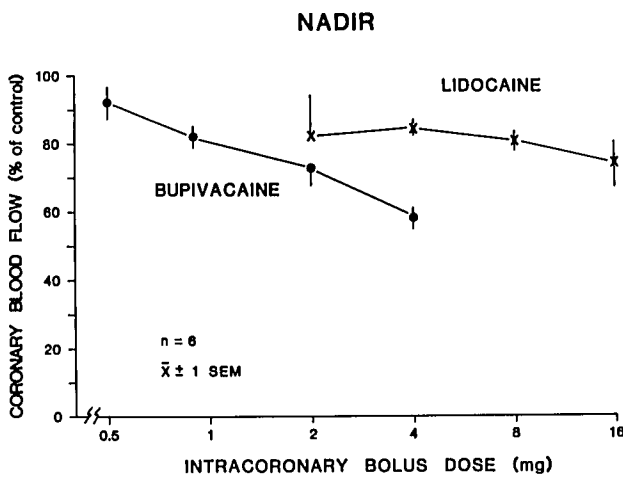


FIG. 5. Coronary blood flow, expressed as a percent of the value obtained just prior to injection of local anesthetic, is shown versus the dose of agent plotted on a log scale. Average coronary blood flow was $0.44\text{--}0.53\text{ ml min}^{-1}\cdot\text{g}^{-1}$ prior to injection. A smaller decrease in flow following high doses of lidocaine than would be expected from the accompanying decrease in systolic contraction probably indicates a small direct vasodilation during lidocaine. Data from six dogs are shown.

25% ($P < 0.05$) following bupivacaine at doses that produced equivalent degrees of depression as lidocaine.

Coronary blood flow measured 40 s following injection was reduced in a dose-dependent fashion by bupivacaine (fig. 5). The magnitude of flow reduction was proportional to myocardial depression. This finding suggests that the flow reduction resulted from lowered myocardial oxygen demand. No relationship between coronary flow and dose of lidocaine was observed.

Discussion

ASSUMPTIONS

The intracoronary doses of local anesthetic used in the present study are proportional to those causing cardiovascular collapse in previous studies. Bolus intracoronary doses of 0.5–4 mg of bupivacaine were delivered to sections of myocardium weighing about 50 g. In comparison, a number of investigators have found that an iv dose of about 20 mg/kg (1 mg per 50 g) is required to cause cardiovascular collapse in dogs.^{5,18}

Although the dose of local anesthetic corresponds reasonably well with that used in prior studies, the peak anesthetic concentration in the blood perfusing the heart may have been as high as 100–2,000 $\mu\text{g/ml}$ because the bolus (0.5–16 mg) was delivered over a 10-s period into 5–8 ml of blood. In contrast, Kasten and Martin found serum bupivacaine levels of 38 $\mu\text{g/ml}$ at the time of death in dogs.¹⁸ The discrepancy between these concentrations may be partially explained by tissue uptake of bupivacaine because a heart:blood concentration ratio of 5.0 was observed by Kasten and Martin.¹⁸

A high blood concentration of these local anesthetics would tend to saturate binding sites of albumin and α_1 -acid glycoprotein and thus lead to a relatively high fraction of unbound drug.¹⁹ No studies of local anesthetic binding have used such high concentrations,²⁰ and so firm estimates of the fraction bound are not available. It seems likely, however, that the difference in protein binding between lidocaine and bupivacaine²⁰ that exists at lower concentrations might be diminished. As a consequence, relatively more bupivacaine may have been unbound and thus available to move into the myocardium than would be the case with lower drug concentration. Such an effect would tend to exaggerate the difference between lidocaine and bupivacaine and enhance the myocardial depression seen with bupivacaine.

A second concern is that bolus administration may have allowed insufficient time for transfer of drug from blood into myocardium. The amount transferred depends on the concentration gradient, the lipid solubility of the

agent, and the transit time through the organ. Bupivacaine's relatively high lipid solubility (heptane:water partition coefficient 27.5 vs. 2.9 for lidocaine)²¹ would favor enhanced movement of this agent into the tissue. In addition, the transit time for lidocaine may have been less because lidocaine, especially at high doses, produced a transient increase in coronary blood flow (fig. 1). The faster transit would tend to reduce the amount of lidocaine that entered tissues. Both mechanisms would tend to exaggerate the differences between agents. Thus, a steady state infusion may have resulted in a lower lidocaine:bupivacaine depression ratio than the 4.9:1 observed.

A third concern is that recirculation of drug may have influenced measurements made toward the end of the experiment. As a guard against systematic bias of this sort, the order of drugs and doses was randomized. In addition, rapid tissue uptake and metabolism of these agents argues against a significant amount of recirculation. The alpha-phase redistribution half-life is 2.7 min for bupivacaine and 1.0 min for lidocaine.²²

CRITIQUE OF THE PREPARATION

The direct effects of local anesthetics on the heart are difficult to determine when the agent is administered intravenously. At low concentrations local anesthetics depress inhibitory pathways in the CNS and cause a mild sympathetic activation.^{23,24} A more prominent sympathetic activation occurs in association with seizures²⁵ and usually leads to hypertension and tachycardia. In addition, a recent study has demonstrated a decrease in arterial blood pressure and heart rate as well as an increase in A-V conduction time when lidocaine and bupivacaine were applied directly to centers in the brain stem.²⁶ Finally, seizures in an unventilated animal rapidly produce hypercarbia, hypoxia, and acidosis, changes that enhance the cardiovascular toxicity of local anesthetics.⁸

In the present study these confounding systemic effects were minimized by direct injection of small doses of agent into a coronary artery. In addition, only about 30% of the left ventricle was exposed to drug, and so overall cardiac function was not dramatically impaired. As a result, homeostatic cardiovascular reflexes were probably not elicited. Direct intercoronary injection of local anesthetics has been employed previously.⁹

Heart rate was controlled at 100 beats/min by ventricular pacing following creation of an A-V heart block by injection of formalin into the A-V node. Heart rate was controlled in an effort to avoid the changes in regional contraction that accompany changes in heart rate.²⁷ Mean arterial blood pressure was controlled as well in an effort to stabilize the global hemodynamic determinants of

myocardial oxygen consumption. These efforts were made so that changes in coronary blood flow could be interpreted. The fact that coronary blood flow decreased along with regional myocardial function following bupivacaine injection is consistent with the local nature of metabolic control of coronary blood flow.

INTERPRETATION

In the present study the magnitude of myocardial depression following intracoronary injection of bupivacaine and lidocaine paralleled their local anesthetic potency. The commonly accepted potency ratio is 4:1 (lidocaine:bupivacaine, L:B),²⁸ and the ratio of the concentrations producing a 50% decrease in regional contraction was 4.9:1. Using different endpoints, other investigators have concluded that the cardiovascular toxicity of bupivacaine is either comparable to its anesthetic potency^{5,6,9} or greatly exceeds its potency.^{8,11-13,29,30} Part of these differences may result from the endpoints used because bupivacaine is more likely to cause A-V conduction blocks and ventricular arrhythmias than is lidocaine.^{4,8,9}

The results of the present study should be compared with the results of other studies in which myocardial depression was the endpoint. Tanz *et al.* determined a 10:1 (L:B) ratio for equivalent degrees of dF/dt in isolated guinea pig hearts,¹¹ and Lynch found that a similar ratio (10:1) caused equal contractile depression in isolated papillary muscles from guinea pigs.¹² Wheeler *et al.* found a 8:1 ratio for depression of contraction of isolated canine heart.³⁰ In contrast, Nath *et al.* studied anesthetized pigs and found that a 4:1 (L:B) ratio produced equivalent decreased in mean arterial blood pressure and dP/dt following intracoronary injection.⁹

Why the results of studies in isolated hearts and those of Nath *et al.*⁹ and the present study differ is not clear. The difference in species (rabbits and guinea pigs vs. pigs and dogs) is one possible explanation because a recent study has demonstrated that sheep are more sensitive to bupivacaine than are dogs.¹⁸ Perhaps the use of nonblood perfusion medium in the isolated preparations is also important.

The duration of myocardial depression following bolus intracoronary injection of local anesthetic was found to be about 25% longer for bupivacaine compared to lidocaine at equal levels of myocardial depression ($P < 0.05$). Although this difference was statistically significant, the clinical relevance of such a difference may be questioned. Such small differences are not likely to account for the clinical impression that longer periods of resuscitation are required in cases of inadvertent bupivacaine overdose.¹ Of importance, however, is the observation that depres-

sion persisted for 10–15 min following the larger doses of both drugs. Clearance of drug from the myocardium in a clinical cardiac arrest could conceivably take even longer because low arterial blood pressure might reduce coronary blood flow.

The present results differ from those of previous studies. For example, Lynch found complete return to control contractile force during washout in isolated papillary muscles following lidocaine but not bupivacaine.¹² Wegrzynowicz found that the duration of myocardial depression in isolated rabbit hearts was markedly prolonged with bupivacaine when compared to equally depressant doses of lidocaine.¹⁴ In addition, the time for membrane voltage change during depolarization to return to normal was fivefold longer after 1 $\mu\text{g}/\text{ml}$ of bupivacaine than after 5 $\mu\text{g}/\text{ml}$ of lidocaine in isolated heart muscle.³¹ The reasons that bupivacaine's duration of effect seems longer in isolated heart muscle preparations than in the present study is not clear. Perhaps binding of the drug to plasma proteins in the present study, an effect that is not possible to replicate in nonblood perfused preparations, hastened removal of bupivacaine from the myocardium.

Coronary blood flow was decreased in proportion to the decrease in regional contraction following injection of bupivacaine. However, flow decreases following lidocaine appeared to be slightly less than predicted on the basis of the accompanying decline in function at larger lidocaine doses. This may reflect a slight direct vasodilation by lidocaine³² that is not present with bupivacaine. A previous study by Tanz *et al.* reported similar decreases in coronary flow with both drugs.¹¹ These flow decreases were accompanied by, and presumably caused by, decreases in myocardial oxygen consumption. In the present study lidocaine elicited a short-lived hyperemia during the first 15–20 s following injection. Flow responses during this period following injection of bupivacaine were less marked (fig. 1). Nath *et al.* failed to find a change in coronary sinus blood flow following intracoronary local anesthetic injection,⁹ but small changes in flow may have been missed because of the relative insensitivity of the thermal-dilution technique used.

LIMITATIONS

The results of this study should be extrapolated to the clinical situation with caution. The study was done in open-chest dogs that were anesthetized with morphine and alpha-chlorolose. These agents may have interacted with the local anesthetics to affect the coronary vascular and myocardial responses. Kasten and Martin recently demonstrated impressive differences in the sensitivity of sheep and dogs to the cardiovascular toxicity of

bupivacaine¹⁸; similar toxicity differences between dogs and humans could well exist. This study also does not address the electrophysiologic effects of the agents, an aspect of demonstrated importance in determining the likelihood and severity of cardiovascular collapse following the iv injection of these agents.^{7,10,29,30}

In summary, direct intercoronary bolus injection of lidocaine and bupivacaine produced regional myocardial depression in proportion to the anesthetic potency of the drugs. The duration of depression was about 25% longer following bupivacaine compared with that following lidocaine. A period of 10–15 min was required for 95% recovery following larger doses of each agent. These findings suggest that direct depression of myocardial contraction is not likely the cause of perceived clinical differences between lidocaine and bupivacaine in the severity or duration of cardiovascular collapse following inadvertent iv administration.

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