Anesthesiology
75:243–251, 1991

The Effects of Local Anesthetics and Epinephrine on Rat Sciatic Nerve Blood Flow

*B. L. Partridge, M.D., D.Phil.**

The effects of topical application of local anesthetics on peripheral nerve blood flow (NBF) were studied in the rat sciatic nerve. Sciatic NBF was measured by laser doppler in 45 adult female Sprague-Dawley rats (90 nerves) after topical application of 25 μl lidocaine and epinephrine, alone and in combination (lidocaine plus epinephrine), as well as bupivacaine, tetracaine, and normal saline, and studied in a randomized, blinded experimental design. NBF changes produced by lidocaine were dose-dependent. Compared with that for saline, blood flow reduction for lidocaine 0.5% was not significant, but it was significant for lidocaine 1.0% at 2–5 min and for lidocaine 2.0% at all time periods after 1 min ($P < 0.05$). Maximum reduction was seen at all concentrations by 5 min after application. Average blood flow reduction at 5 min was 7% for lidocaine 0.5%, 12% for lidocaine 1.0%, and 18% for lidocaine 2.0%. Epinephrine also produced dose-dependent changes in NBF. Epinephrine 2.5 μg/ml produced a transient 20% increase in NBF lasting 2–3 min ($P < 0.05$), followed by a return to baseline. Epinephrine 5.0 μg/ml and epinephrine 10.0 μg/ml produced reductions of 20% and 35%, respectively ($P < 0.05$), which lasted throughout the study. The effects of each of the three concentrations were significantly different from the others. The combination of lidocaine plus epinephrine resulted in synergistic reduction of NBF for all drug concentrations ($P < 0.05$). For example, although lidocaine 2.0% reduced NBF by 18% and epinephrine 5.0 μg/ml reduced NBF by approximately 20%, lidocaine plus epinephrine (2.0% plus 5 μg/ml) decreased NBF by 60% ($P < 0.05$). Although increasing concentrations of lidocaine resulted in significantly greater reductions in NBF ($P < 0.05$), increasing concentrations of bupivacaine resulted in progressively less reduction ($P < 0.05$). NBF in bupivacaine- and lidocaine-treated nerves was significantly lower than that in nerves treated with tetracaine or normal saline at all time periods after 5 min. In the doses used, tetracaine did not produce any change in peripheral NBF at any of the time periods measured. (Key words: Circulation: peripheral nerve blood flow. Local anesthetics: bupivacaine; lidocaine; tetracaine. Local anesthetic toxicity. Regional anesthesia.)

PERIPHERAL NERVE INJURY is an infrequent but sometimes devastating complication of regional and general anesthesia. In the absence of direct surgical trauma or use of tourniquets, neural ischemia has been suggested as the cause of most nerve injuries during general anesthesia. Ischemia may be caused by compression, stretching, edema, hypotension, or a combination of these.[1–3] Nerve injury during regional anesthetics may occur by these mechanisms, but it also may result from direct nerve trauma from needles,[4] toxicity of local anesthetics,[5,6] and preservatives.[7] Additionally, ischemia might result from changes in peripheral nerve blood flow (NBF) caused by the local anesthetics or adjuvant vasopressors. Reduced NBF has been reported in edematous neuropathies with increased endoneurial fluid pressure[5,8,9] and in diabetic neuropathies.[10] Acute reduction of NBF has been associated with centrifascicular fiber degeneration in human and animal models.[11] In addition, a recent computer simulation of endoneurial fluid pressure supports this effect on NBF.[12]

The effect of local anesthetics and vasoconstrictors applied directly to the nerve, as occurs during regional anesthetic techniques, has not been fully elucidated. To influence NBF, local anesthetics may act directly on the smooth muscle of epineurial and endoneurial blood vessels[4] or indirectly on the vaso nervorum supplying these vessels.[13,14] In previous studies, Myers and Heckman[15] demonstrated that lidocaine and epinephrine reduced NBF when applied topically to the sciatic nerve in a rat model.

Epinephrine is used commonly as an adjuvant to local anesthetics to reduce systemic toxicity and extend the effective length of anesthesia produced, by reducing uptake by the systemic circulation. Administration of an adjuvant vasopressor to local anesthetics could affect peripheral NBF significantly during regional anesthesia. Selander *et al.*[4] have shown that the addition of epinephrine to local anesthetics increases the nerve damage caused by direct intrafascicular injection of local anesthetics. Topical administration of epinephrine reduces peripheral NBF[4,15] and may contribute to continued edema and permanent injury after such injections. Local anesthetics, and perhaps their preservatives, appear to be neurotoxic in a dose-dependent fashion.[7,16,17] The mechanism for this appears to be production of endoneurial edema, but the effect of local anesthetics other than lidocaine on NBF as a proximal cause of nerve injury has not been studied.

Evidence from studies of the effects of local anesthetics on muscle blood flow (MBF) suggests that there may be differences in the effects of various agents and that these differences may be dose-dependent.[18–20] In this study, I

* Assistant Professor of Anesthesiology.

Received from the Department of Anesthesiology, University of California at San Diego, and VA Medical Center, San Diego, California. Accepted for publication March 29, 1991. Supported by an American Society of Anesthesiologists Starter Grant Award and a Department of Veterans Affairs Merit Review Grant. Presented in part at the Annual Meeting of the International Anesthesia Research Society, Honolulu, Hawaii, 1990.

Address reprint requests to Dr. Partridge: Anesthesiology Service (125), Department of Veterans Affairs Medical Center, 3350 La Jolla Village Drive, San Diego, California 92161.

examined the effects of three local anesthetics (lidocaine, bupivacaine, and tetracaine) and an adjuvant vasoconstrictor (epinephrine) on sciatic NBF in the rat.

Materials and Methods

After institutional Animal Care Committee approval, sciatic NBF was measured in 45 adult, female Sprague-Dawley rats (90 nerves), studied in a randomized, blinded experimental design. Animals were fasted overnight and then weighed and anesthetized with intraperitoneal pentobarbital (50 mg/kg) and diazepam (20 mg/kg) in saline.[15] After induction of anesthesia, the animals were placed on a heating pad and covered with a Mylar® shield to prevent convective heat loss. Rectal temperature was monitored continuously (Yellow Springs Thermometer, YSI), and core temperature was maintained between 35° and 36° C. The hindquarters were shaved, and the sciatic nerves were exposed bilaterally by reflection of the overlying muscles. Extreme care was taken to avoid trauma to the epineurial circulation.

Nerve blood flow was measured with a TSI® Laser Doppler Flowmeter (LDF; TSI model BPM 403A) 0.5-mm probe placed in gentle contact with the sciatic nerve by micromanipulator. The LDF probe was placed under microscopic visualization, and care was taken to position the probe so that it did not overlie visible epineurial vessels directly. Thus, LDF measurements more accurately reflected average capillary blood flow in the tissue immediately underlying the probe in an area that was approximately 0.5 mm^3.[15] A small amount of standard electrode gel provided optical coupling between the laser and tissue. Previous studies have demonstrated good correlation between NBF measured by LDF and other methods,[21] and work in this laboratory and others[15] has demonstrated that reliable, steady-state recordings could be made in this preparation. Blood pressure was not measured in these experiments, avoiding the greater physiologic trespass and time required for cannulation of the arterial circulation. Therefore, the results are directly comparable to those of previously published studies. As described by Myers and Heckman,[15] unpublished experiments in this laboratory have demonstrated that blood pressure remains stable with the intraperitoneal anesthesia used here. In addition, studies in this laboratory performed before and after the current study, in which both the common carotid artery and the internal jugular vein were cannulated, demonstrate physiologic stability of the preparation and NBF recordings. For example, figure 1 shows stable blood pressure and sciatic NBF recordings over 3 h in an animal with anesthesia and NBF recordings made as described above.

After exposure of the sciatic nerve and application of the coupling gel and flow probe, the animal was allowed to stabilize for 5–10 min; then the LDF measurements were begun. The TSI® LDF was set to provide a 5-s moving average of instantaneous NBF recordings. (Instantaneous recordings demonstrate respiratory and cardiac variation.) Stable recordings for individual nerves were defined as output ranges for an individual nerve of no greater than ±1 mV over a 5-min period. After 5 min of stable recordings were obtained, 25 μl coded experimental solution was applied 0.5 cm proximal to the recording site, and NBF was recorded continuously for 40 min. At that time, the nerve was washed with 2–3 ml normal saline, and the recordings were continued for an additional 20 min.

Experimental and washout solutions were prewarmed in a constant-temperature bath at 36° C. Experimental

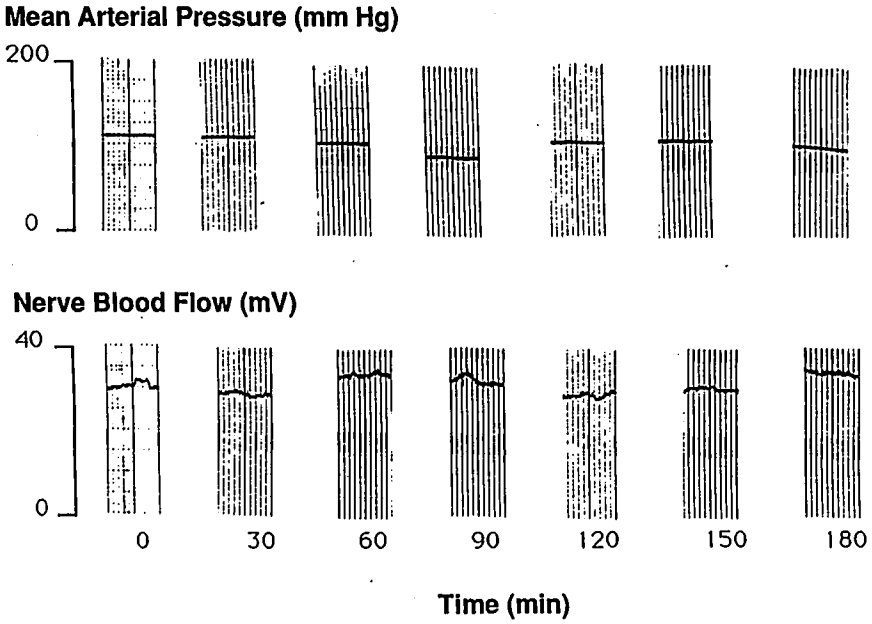

FIG. 1. Mean arterial blood pressure and sciatic nerve blood flow remain stable over a 3-h period in an anesthetized rat. Shown are tracings from a single animal anesthetized as described in Materials and Methods with, in addition, the right common carotid and left internal jugular vein cannulated. Mean blood pressure was recorded with Spectramed™ transducers and displayed on a Hewlett Packard™ strip chart recorder. Little change is noted over the 3-h recording period. Time 0 refers to the time after stable NBF recordings were obtained, approximately 20 min after induction of anesthesia. The animal received a second ip dose of anesthetic just prior to the recording at 90 min.

solutions were applied by droplet from a microliter syringe. Washout was performed by gently dripping 2–3 ml nonpreservative saline (Lyphomed®) across the nerve from a 3-ml syringe fit with a 22-g, blunt-tipped needle and absorbing the excess solution with a cotton-tipped swab placed nearby. The following were tested: lidocaine (Astra Pharmaceutical Products, Westborough, MA) 0.5%, 1.0%, and 2.0%; epinephrine (Parke-Davis; Morris Plains, NJ) 2.5, 5.0, and 10 μg/ml; lidocaine 0.5%, 1.0%, and 2.0% with epinephrine 5 μg/ml (commercial preparation, Astra); bupivacaine (Winthrop Pharmaceuticals; New York, NY) 0.25%, 0.5%, and 0.75%; tetracaine (Winthrop) 0.5% and 1.0%; and nonpreservative saline (Lyphomed®) control. (See table 1 for drug formulations.) Six nerves were tested per treatment. Lidocaine, lidocaine plus epinephrine, bupivacaine, and normal saline were stored at room temperature; and tetracaine was kept refrigerated until the morning of the experiment. Lidocaine and bupivacaine were applied in commercially available preparations. Epinephrine was diluted with normal saline to the desired concentration on the morning of the experiment, and tetracaine 0.5% was prepared similarly by dilution of commercially prepared tetracaine 1.0% with normal saline. Only one test solution was applied to any sciatic nerve. Solutions were administered in random order in a double-blind experimental design.

After readings were taken from one sciatic nerve, the wound was closed, the animal turned over, the sciatic nerve on the opposite side exposed, and a second test solution applied after a minimum of 1 h from the end of the original recordings (and 2 h after the initial application of study drug to the opposite side). Before the second nerve was dissected, a second injection of pentobarbital (25 mg/kg) and diazepam (10 mg/kg) in saline was administered intraperitoneally.

Although some evidence suggests that NBF can be read directly from the laser doppler readings,[21] in this study NBF data were recorded as millivolts (table 2) and expressed as percentage of control for each nerve. Direct calibration of laser doppler flow measurements has been attempted,[22] with flow reported in milliliters per gram per minute, but this has not been done for NBF, so data are reported here as proportions of control flow. Thus, percentage changes in NBF are shown, but no representations are made regarding absolute values of flow. Techniques such as hydrogen polarimetry and microsphere determination of blood flow provide only intermittent measurements. Laser doppler flowmetry presents a distinct advantage over other more quantitative methods of NBF measurement in that it allows continuous recording of NBF, and one need not guess in advance when the maximum responses will occur to allow these to be measured.

The extremely small quantities of study drugs administered (less than 0.5 mg local anesthetic and/or less than 0.25 μg epinephrine) make it unlikely that systemic uptake of local anesthetics or epinephrine contribute to the results seen here; nonetheless, medications were administered in a randomized, blinded fashion so that any effects of order or interaction of local anesthetics/epinephrine should be distributed randomly among treatment groups. As stated previously, the flow probe was placed with microscopic guidance to avoid epineurial vessels. Because starting values of NBF still varied between nerves by as much as 40%, presumably as a result of the vasculature underlying the flow probe, analysis was performed on NBF as a function of control values for individual nerves. Data were analyzed by repeated-measures analysis of variance, with significant interactions investigated by Neuman-Keuls. A P value less than 0.05 was considered significant.

Results

No difference in NBF was observed between groups before application of the study drugs (table 2). Table 2

TABLE 1. Characteristics of Experimental Solutions

Experimental Drug	Concentration	Manufacturer	Sodium Metabisulfite mg/ml	Methylparaben mg/ml
Lidocaine	0.5%	Astra	0	1.0
	1.0%	Astra	0	1.0
	2.0%	Astra	0	1.0
Lidocaine + epinephrine	0.5%	Astra	0.5	1.0
	1.0%	Astra	0.5	0.0
	2.0%	Astra	0.5	0.0
Epinephrine	2.5 μg/ml	Parke-Davis	0.0025	
	5.0 μg/ml	Parke-Davis	0.005	
	10.0 μg/ml	Parke-Davis	0.01	
Bupivacaine	0.25%	Winthrop	0	1.0
	0.50%	Winthrop	0	1.0
	0.75%	Winthrop	0	1.0
Tetracaine	0.5%	Winthrop	2.0	0
	1.0%	Winthrop	2.0	0
Saline	0.9%	Lyphomed	0	0

TABLE 2. Laser Doppler Flow Values

Drug	Concentration	Time (min) 0 (Control)	5	10	20
Saline	0.9%	28.7 ± 2.9	30.3 ± 2.3	30.6 ± 2.9	30.2 ± 2.7
Lidocaine	0.5%	27.9 ± 2.3	26.5 ± 3.8	26.6 ± 3.5	26.6 ± 3.7
Lidocaine	1.0%	27.8 ± 2.4	25.6 ± 2.2	25.3 ± 2.6	25.8 ± 2.5
Lidocaine	2.0%	33.3 ± 1.3	27.4 ± 2.8	27.3 ± 2.7	27.4 ± 2.9
Epinephrine	2.5 μg/ml	32.4 ± 1.7	34.6 ± 1.9	33.7 ± 2.0	31.6 ± 2.8
Epinephrine	5.0 μg/ml	32.2 ± 1.2	26.9 ± 3.8	26.5 ± 4.4	26.8 ± 4.3
Epinephrine	10.0 μg/ml	28.0 ± 1.3	19.5 ± 2.9	19.6 ± 2.6	16.8 ± 3.6
Lidocaine/epi	0.5%	28.3 ± 1.6	19.5 ± 3.5	21.1 ± 3.9	20.6 ± 4.2
Lidocaine/epi	1.0%	31.3 ± 3.8	22.6 ± 7.2	22.1 ± 7.1	21.7 ± 7.3
Lidocaine/epi	2.0%	29.5 ± 1.7	12.3 ± 2.8	11.5 ± 2.5	11.2 ± 2.5
Bupivacaine	0.25%	38.7 ± 3.3	24.7 ± 2.2	26.0 ± 2.1	25.5 ± 2.3
Bupivacaine	0.50%	28.7 ± 1.6	20.4 ± 2.9	21.0 ± 2.3	20.7 ± 2.6
Bupivacaine	0.75%	30.9 ± 1.6	28.0 ± 3.2	26.8 ± 3.5	23.9 ± 4.7
Tetracaine	0.5%	31.4 ± 2.4	32.0 ± 2.3	31.4 ± 2.6	33.8 ± 2.7
Tetracaine	1.0%	30.7 ± 1.2	31.9 ± 0.8	31.9 ± 1.4	32.6 ± 1.3

Flow values are millivolts, mean ± SEM.

shows the mean NBF values (± standard error of the mean) in millivolts for each of the 15 study groups before and at 5, 10 and 20 min after topical application of study drugs. Application of nonpreservative saline produced no significant changes in NBF in the experimental animals. The average NBF readings were 28.7 ± 3 mV before and 30.3 ± 2 mV 5 min after application of control solutions. Placement of the LDF probe over the sciatic nerve produced NBF outputs of 28–45 mV in the control situation. As described above, comparisons between treatments were made on the basis of proportional changes in NBF.

Comparison of NBF from first and second nerves tested in each animal produced no systematic differences ($P = 0.65$), suggesting that there was not a significant order effect in the application of local anesthetics or epinephrine to the sciatic nerves. Because of this, data from the six replications of each experimental treatment were averaged, and the figures follow. Statistics were calculated for individual experimental replications.

Changes in NBF produced by lidocaine appear to be dose-dependent (fig. 2). Compared with that for saline, reduction in blood flow for lidocaine 0.5% was not significant, but flow reduction was significant for lidocaine 1.0% at 2–5 min ($P < 0.05$) and 2.0% at all time periods after 1 min ($P < 0.05$). Maximum reduction was seen at all concentrations within 5 min after application. NBF returned to control values in the 1.0% group by 10 min. Values for 0.5% and 1.0% were not significantly different after 5 min. Blood flow reduction was small but consistent. Average blood flow reduction at 5 min was 7% for lidocaine 0.5%, 12% for lidocaine 1.0%, and 18% for lidocaine 2.0%—a significant trend with concentration ($P < 0.01$). No recovery was seen in the 2.0% group after 60 min, despite washout with normal saline at 40 min (fig. 2).

Epinephrine produced dose-dependent changes in NBF that were much larger than those produced by lidocaine alone (fig. 3). Topical application of 25 μl epinephrine 2.5 μg/ml (1:400,000) resulted in a transient 20% increase in NBF lasting 2–3 min ($P < 0.05$), followed by a gradual return to baseline over 10 min. NBF was not significantly different from the control values of each nerve or the values of the saline control group after 5 min. Epinephrine 5.0 μg/ml and 10.0 μg/ml produced NBF values significantly less than control for all time periods after 3 min.

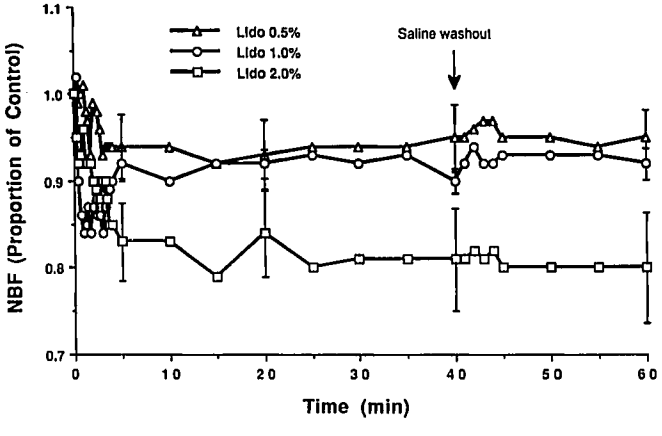

FIG. 2. Effect of topical lidocaine (Lido) on sciatic nerve blood flow (NBF) in the rat. Results shown are the mean values (±SEM) for blood flow for six animals for each treatment, expressed as a function of control values. Time 0 represents the time of application of 25 μl test solution (saline, lidocaine 0.5%, lidocaine 1.0%, or lidocaine 2.0%) to the sciatic nerve. NBF is not significantly different from control in the 0.5% group but reaches significance at 2–5 min for the 1.0% group and for all time periods after 1 min for the 2.0% group. The 2.0% group also showed significant reductions compared to the 0.5 and 1.0% groups for all time periods after 5 min. NBF reductions continue for 1 h, even with attempts to "wash out" the local anesthetic at 40 min. n = 6 nerves per treatment.

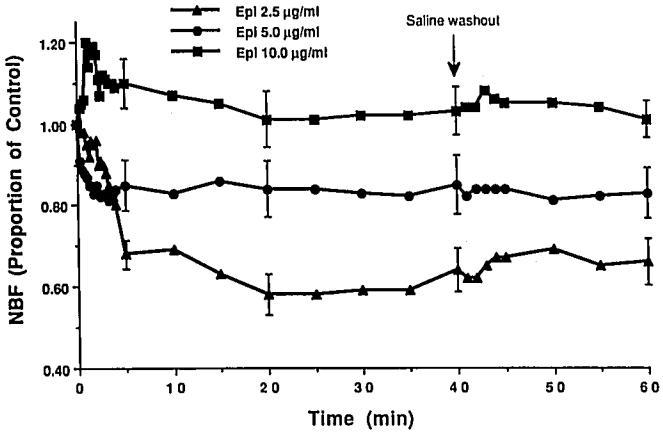

FIG. 3. Effect of topical epinephrine (Epi) on sciatic nerve blood flow (NBF) in the rat. A dose-dependent reduction in mean NBF is apparent. Epinephrine 2.5 µg/ml resulted in a transient but significant increase in NBF, lasting approximately 2–3 min, followed by a gradual return to baseline. No difference between experimental and control nerves is seen after 5 min. Administration of epinephrine 5.0 or 10.0 µg/ml resulted in reduction of NBF of approximately 20 and 35%, respectively. Differences from control were significant for all time periods after 3 min. Differences between treatments became significant after 5 min. No recovery was seen with washout. n = 6 nerves per treatment.

Epinephrine 5.0 µg/ml (1:200,000) and epinephrine 10.0 µg/ml (1:100,000) produced NBF reductions of 20% and 35%, respectively ($P < 0.05$), which lasted throughout the study. As with lidocaine, described above, the maximum effect of epinephrine was observed within 5 min and remained fairly stable for the next 55 min of recording. Washout at 40 min produced no significant recovery for either group, although there was a slight trend toward recovery in the 10.0 µg/ml group (fig. 3). Each of the three concentrations was significantly different from the others for all time periods after 5 min ($P < 0.05$).

The combination of lidocaine plus epinephrine (5.0 µg/ml) resulted in the synergistic reduction of NBF for all drug concentrations ($P < 0.05$, fig. 4). For example, although NBF was not significantly different from the saline control after topical application of lidocaine 0.5%, and topical application of epinephrine 5.0 µg/ml reduced NBF by approximately 20%, the combination of lidocaine plus epinephrine (0.5% plus 5 µg/ml) resulted in a transient but significant increase in NBF lasting approximately 3 min, followed by a reduction to approximately 70% of control ($P < 0.05$, fig. 4). Similar synergistic results are seen for lidocaine 1.0% and 2.0% ($P < 0.05$, different from control and from lidocaine alone for all time periods after 5 min). With greater concentrations of lidocaine, the transient increase in NBF was not observed. Significant reductions in NBF were seen for the lidocaine–epinephrine combinations of 1.0% and 2.0% within 1 min after application and continued for more than 60 min. The maximal reductions in NBF, observed with lidocaine 2% plus epinephrine 5.0 µg/ml, were 60% for periods after 5 min. Saline washout at 40 min did not affect the reduction in NBF.

Significant differences were observed between local anesthetics in their effects on NBF. Like lidocaine, bupivacaine caused significant dose-dependent reductions in NBF compared with control saline (fig. 5). Increasing concentrations of lidocaine resulted in significantly greater reductions in NBF; ($P < 0.05$) however, increasing concentrations of bupivacaine resulted in progressively less reduction ($P < 0.01$). Thus, bupivacaine 0.25% produced the greatest reduction in NBF (approximately 35%) at 5 min, whereas bupivacaine 0.5% was followed by reductions of 25% and bupivacaine 0.75% was followed by reductions of 15% (at 10 min) to 20% (from 15 to 40 min). NBF values for 0.25% and 0.5% were significantly different at 5 and 10 min ($P < 0.05$) but not significantly different after that. Unlike the situation for lidocaine, epinephrine, or the combination of the two, washout of bupivacaine with saline at 40 min resulted in significant increases in NBF, to approximately 90% of control (a value that still was significantly different from saline controls, however [$P < 0.05$]; fig. 5).

In the doses used, tetracaine did not cause a significant change in peripheral NBF at any of the time periods measured (fig. 6). As in saline-treated nerves (also shown in figure 6), mean NBF increased slightly (6–8%) but not significantly ($P < 0.23$). The NBF in bupivacaine-treated nerves was significantly lower than for those treated with tetracaine or saline at all time periods after 5 min, until

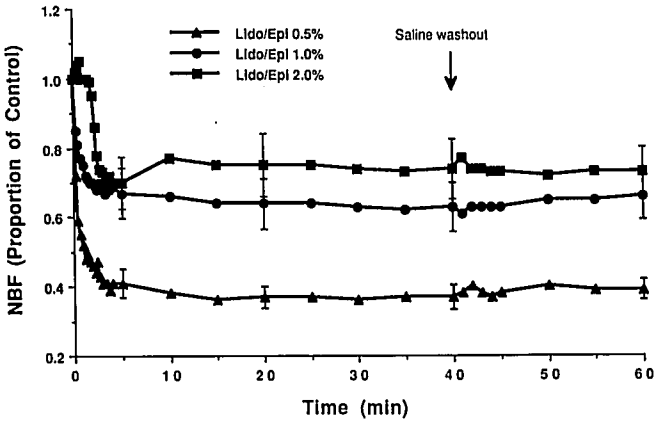

FIG. 4. Synergistic effect of topical application of lidocaine and epinephrine (Lido/Epi) on nerve blood flow (NBF). Lidocaine (0.5, 1.0, and 2.0%) plus epinephrine 5 µg/ml (1:200,000) resulted in significant augmentation of the reduction seen with either lidocaine or epinephrine alone. A transient but significant increase in NBF is seen with the lowest concentration of lidocaine, followed by reduction of NBF of approximately 20%. Significant differences between treatments and between treatments and control are seen for all time periods after 2 min. No recovery was seen with washout. n = 6 nerves per treatment.

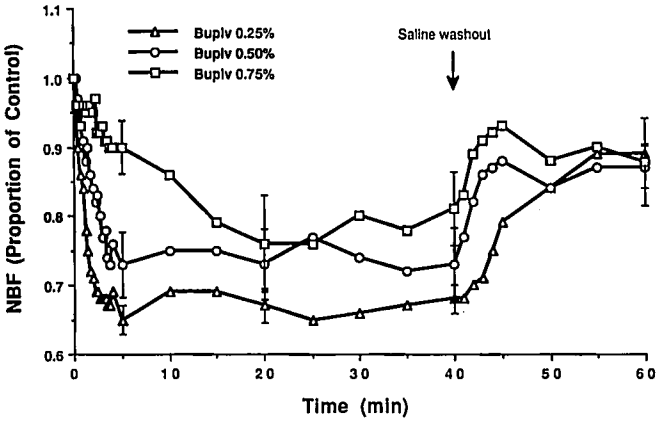

FIG. 5. Effect of topical application of bupivacaine (Bupiv) on nerve blood flow (NBF). A dose-dependent reduction in NBF is apparent. Unlike lidocaine (fig. 1), however, the lowest concentrations of bupivacaine resulted in the greatest reductions in NBF. Bupivacaine 0.25% resulted in reduction of NBF by 20% at 2 min ($P < 0.05$, compared to control) and 35% at 5 min ($P < 0.05$ compared to control and to bupivacaine 0.5 and 0.75%.) All three concentrations of bupivacaine resulted in significant reductions at all time periods after 5 min. Washout of the nerve preparation with saline at 40 min resulted in immediate increases in NBF, with return to approximately 90% of control values. n = 6 nerves per treatment.

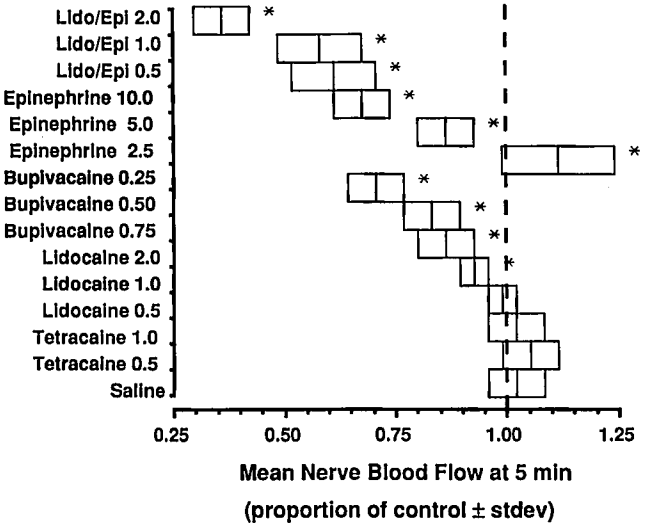

FIG. 7. Mean nerve blood flow (±SD) for all treatments at 5 min after topical administration. Significant changes from control are marked by an asterisk. All treatments except lidocaine 0.5% and tetracaine 0.5 and 1.0% produced significant reductions in NBF at 5 min. The greatest reductions were observed for treatment with lidocaine 2.0% plus epinephrine 5.0 μg/ml. n = 6 nerves per treatment.

the time of attempted washout ($P < 0.05$; see fig. 7); and the NBF for lidocaine-treated nerves (1.0% and 2.0%) was significantly less for all time periods up to 60 min ($P < 0.05$).

Discussion

Small but significant reductions in NBF were seen after topical application of lidocaine to rat sciatic nerve. Greater reductions were seen with epinephrine, and the combination of lidocaine 2.0% plus epinephrine 5.0 μg/ml resulted in a synergistic reduction totaling 60%. Small, transient increases in NBF were observed with a lower concentration of epinephrine (2.5 μg/ml). Bupivacaine produced dose-dependent reductions in NBF, with the lowest concentrations (0.25%) producing the greatest reduction and the highest concentrations (0.75%) producing the least. Tetracaine 0.5% and 1.0% did not produce a significant change in NBF. Figure 7 summarizes the results obtained at 5 min in these experiments.

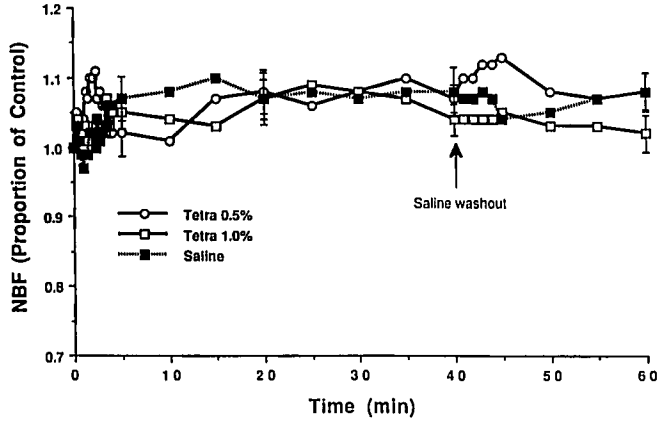

FIG. 6. Effect of topical application of tetracaine (Tetra) and nonpreservative normal saline on nerve blood flow (NBF). No significant change in NBF was observed after topical application of tetracaine 0.5 and 1.0%. Similarly, no significant change is noted after application of normal saline. n = 6 nerves per treatment.

In a nonblinded study, Myers and Heckman[15] reported decreases in NBF after topical application of 200 μl 1.0% and 2.0% lidocaine solutions. Although the amount of lidocaine applied to the nerve was eight times greater than that used here and resulted in considerable bathing of the surrounding tissue, the results were similar. They showed greater reductions in NBF at the two concentrations studied than those reported here, however—presumably because of the greater dose of medication given (as opposed to simply the concentration of the solutions). This leaves open the question of the optimal volume of local anesthetics to be applied in this model. On the one hand, greater reductions of NBF may be seen with larger volumes, but, on the other hand, significant amounts of drug will spill off the nerve preparation and onto nearby muscle. Application of larger doses of local anesthetics might have altered the picture seen, because there appear to be both concentration and dose effects. The interaction between dose and concentration remains to be more fully elucidated, particularly with respect to issues of nerve

toxicity.[6,7] It is interesting that maximal reductions in NBF observed in the two studies were similar, suggesting an absolute minimum that can be produced by vasomotor responses. Such a finding suggests a ceiling effect of local anesthetic and adjuvant drugs and argues for minimizing doses used to those that only produce the desired anesthetic effect.

In the studies described here, tetracaine caused no significant change in NBF, whereas topical application of bupivacaine and lidocaine produced dose-dependent changes in NBF. Whether addition of epinephrine to tetracaine or bupivacaine would produce greater or lesser effects than its addition to lidocaine is not known. It is possible that the tetracaine solutions used in this study had lost potency, but that is unlikely because they were refrigerated until just before use. The relationship between NBF and nerve function is not yet well established. Dramatic reductions in NBF seen after topical epinephrine may explain in part the clinical finding that epinephrine reduces systemic uptake of local anesthetics,[23,24] thereby increasing their potency and duration.[25] Although the concentration of local anesthetics was similar to that of anesthetics used clinically, the amount of drug applied was considerably less that that usually used for regional nerve blocks. The amount of drug used here was sufficient to completely abolish compound nerve action potentials from rat sciatic nerves exposed as in the current study (M. Kalichman, unpublished results). This suggests that very small amounts of local anesthetic are sufficient to completely block nerve transmission—if the anesthetic is applied directly to the nerve—and that the much greater volumes used clinically allow the drug to diffuse toward the nerves if the needle is not placed directly adjacent to them. Larger injected volumes, however, must carry a greater risk of systemic as well as local toxicity.

In the absence of a preexisting nerve abnormality or altered blood flow, the reduction in NBF after single applications of local anesthetics in clinical practice seems unlikely to be the cause of significant, long-lasting peripheral nerve damage. In healthy patients, differences between local anesthetics in their effects on NBF thus may not matter a great deal. Addition of epinephrine as an adjuvant, however, may present a greater risk, because the effects of epinephrine on NBF are considerably greater than those produced by local anesthetics. For people with preexisting nerve abnormalities and altered peripheral blood flow, such as might occur in patients with diabetic neuropathies, smaller incremental changes in peripheral NBF produced by local anesthetics and adjuvant vasopressors may be important.

The anesthetic effects of the local anesthetics used here last only a few hours. (Tourniquets that completely eliminate blood flow are applied routinely for similar periods). The rate of recovery of NBF is not known, however. In the experiments reported here, NBF remained depressed at 1 h after topical application of local anesthetics.

Local anesthetics might be expected to increase peripheral NBF if they acted only on the smooth muscle of epineurial arterioles, causing vasodilatation. On the other hand, at least two factors may decrease NBF: reduction of metabolic needs of the nerve after blockade[26,27] and local anesthetic blockade of the vaso nervorum supplying the epineurial circulation. Evidence that each of these mechanisms may be occurring is seen with the dose-dependent effects of lidocaine, bupivacaine, and epinephrine, each of which may increase or decrease NBF, depending on the concentration and dose. Competing effects on NBF with initial vasodilation followed by vasoconstriction may result from two types of biphasic response—one concentration dependent and the other time dependent. The latter response may result in transient increases in NBF, followed by decreases as the anesthetic takes effect, or may result from opposing results of multiple effects of local anesthetics. Concentration- and time-dependent effects of local anesthetics on NBF may result from opposing consequences of blockade of the vaso nervorum (resulting in vasoconstriction), blockade of receptors located on the epineural blood vessels (resulting in vasodilation), and, possibly, Ca-channel-blocking properties of local anesthetics affecting arteriolar muscle directly.[20] These effects must be differentiated from the effects of blocking the sympathetic innervation either centrally or more peripherally. For instance, at low concentrations, lidocaine and bupivacaine potentiate the effects of sympathetic stimulation to produce vasoconstriction of isolated blood vessels from rabbit ear, whereas at high concentrations they inhibit the effects of sympathetic stimulation.[20] In the absence of hypovolemia, central sympathectomy should produce vasodilation and increase NBF.

As in the previous study by Myers and Heckman, data presented here support the idea that responses for lidocaine may be biphasic; they observed an initial increase in NBF with low concentrations of lidocaine, followed by a decrease in NBF.[15] We observed similar effects in some animals, but no significant effect was seen in the group as a whole for the blinded study described here.

A significant biphasic response to low concentrations of epinephrine and to the combination of lidocaine 0.5% plus epinephrine 5 μg/ml was observed, however. It is interesting that, although epinephrine 5.0 μg/ml did not produce a transient increase in NBF, the combination of 5.0 μg/ml with lidocaine 0.5% did so. Epinephrine previously has been shown to decrease NBF through adrenergic vasoconstriction of epineurial vessels.[14] Meisheri and Van Breeman have demonstrated beta receptors in the smooth muscle of rabbit aorta,[28] and these may be present in the adrenergic supply to the epineurial vessels or the vaso nervorum supplying them. The observation that 2.5

μg/ml epinephrine produced a transient increase in NBF suggests that beta effects predominate at the low dose. At higher epinephrine doses, alpha effects appear to predominate, reducing NBF. Authors previously have mentioned adrenergic nerve terminals located along epineurial and perineurial but not endoneurial blood vessels.[13,14] These are presumably susceptible to control by agents such as epinephrine, whereas the endoneurial circulation is not.

Johns *et al.* reported results similar to those in this study for blood flow in arterioles of a rat cremaster muscle preparation.[18,19] At low concentrations of a local anesthetic (1.0–1,000 μg/ml lidocaine), they observed a reduction in cremaster MBF, but they observed an increase in MBF at higher concentrations of lidocaine corresponding to those used clinically (10,000 μg/ml or 1%). Similar results were observed with bupivacaine.[19] Increasing concentrations of bupivacaine from 10^{-2} to 10^{2} μg/ml resulted in progressive vasoconstriction, whereas even higher concentrations ($1.0–2.5 \cdot 10^{3}$ μg/ml) resulted in vasodilation of precapillary arterioles in the rat cremaster muscle preparation.

By contrast, in two other studies, skin capillary blood flow (SBF) increased after administration of lidocaine and bupivacaine in concentrations similar to those investigated here.† When local anesthetics were injected subcutaneously or intradermally in human volunteers, the lowest concentrations of bupivacaine and highest concentrations of lidocaine had the greatest effects.†[29] SBF increases in response to a needle stick or injection of saline; local anesthetics appear to increase the response, whereas epinephrine decreases it.†

The effects of local anesthetics on spinal cord and dural blood flow were investigated by Kozody *et al.*[30–32] They found that spinal cord blood flow was increased by lidocaine and tetracaine but decreased by bupivacaine (20 mg 0.4% solution). Addition of epinephrine prevented the vasodilation produced by tetracaine and lidocaine but had no effect on the decrease in blood flow produced by bupivacaine.[30–32]

Dissimilarities in lipid solubility between agents (with tetracaine significantly more lipid soluble than lidocaine or bupivacaine) do not account for the different effects seen in various tissues, although they may affect the latency of onset, especially in studies of spinal cord blood flow.[32] The significant difference of the results reported here for peripheral NBF in comparison with those for spinal cord blood flow, MBF, and skin blood flow points to the difficulty in generalizing about the effects of local anesthetics from one organ to another. Thus, the frequent use of centrally acting vasopressors or production of a "sympathectomy" to increase peripheral perfusion after reimplantation or grafting may have quite different effects on NBF than on MBF and SBF. Additional studies are indicated to address the effects of centrally acting vasoactive drugs on peripheral NBF.

The author thanks D. Kon, B.S., for assistance with the experiments, and R. Myers, Ph.D., and M. Kalichman, Ph.D., for providing assistance and encouragement with this project.

References

1. Powell HC, Myers RR: Pathology of experimental nerve compression. Lab Invest 55:91–100, 1986
2. Dornette WH: Compression neuropathies: Medical aspects and legal implications. Int Anesthesiol Clin 24:201–229, 1986
3. Lundborg G, Myers R, Powell H: Nerve compression injury and increased endoneurial pressure: A "miniature compartment syndrome." J Neurol Neurosurg Psychiatry 46:1119, 1983
4. Selander D, Brattsand R, Lundborg G, Nordborg C, Olsson Y: Local anesthetics: Importance of mode of application, concentration and adrenaline for the appearance of nerve lesions. Acta Anesthesiol Scand 23:127–136, 1979
5. Myers RR, Kalichman MW, Reisner LS, Powell HC: Neurotoxicity of local anesthetics: Altered perineurial permeability, edema, and nerve fiber injury. ANESTHESIOLOGY 64:29–35, 1986
6. Henn F, Bratsand R: Some pharmacological and toxological properties of a new long acting analgesic LAC-43 (Marcaine) in comparison with mepivacaine and tetracaine. Acta Anesthesiol Scand [Suppl] 21:9–30, 1966
7. Kalichman MW, Powell HC, Reisner LS, Myers RR: The role of 2-chloroprocaine and sodium bisulfite in rat sciatic nerve edema. J Neuropathol Exp Neurol 45:566–575, 1986
8. Myers RR, Mizisin AP, Powell HC, Lampert PW: Reduced nerve blood flow in hexachlorophene neuropathy: Relationship to elevated endoneurial fluid pressure. J Neuropathol Exp Neurol 41:391–399, 1982
9. Myers RR, Powell HC: Galactose neuropathy: Impact of chronic endoneurial edema on nerve blood flow. Ann Neurol 16:587–594, 1984
10. Low PA: Recent advances in the pathogenesis of diabetic neuropathy. Muscle Nerve 10:121–128, 1987
11. McManis PG, Low PA: Factors affecting the relative viability of centrifascicular and subperineurial axons in acute peripheral nerve ischemia. Exp Neurol 99:84–95, 1988
12. Myers RR, Murakami H, Powell HC: Reduced nerve blood flow in edematous neuropathies: A biomechanical mechanism. Microvasc Res 32:145–151, 1986
13. Apenzeller O, Dhital KK, Cowen T, Burnstock G: the nerves of the blood vessels supplying blood to nerves: The innervation of the vaso nervorum. Brain Res 304:383–386, 1984
14. Selander D, Mansson LG, Karlsson L, Svanik J: Adrenergic vasoconstriction in the peripheral nerves of the rabbit. ANESTHESIOLOGY 62:6–10, 1985
15. Myers RR, Heckman H: Effects of local anesthesia on nerve blood flow: Studies using lidocaine with and without epinephrine. ANESTHESIOLOGY 71:757–762, 1989
16. Gissen AJ, Datta S, Lambert D: The chloroprocaine controversy. I. A hypothesis to explain the neural complications of chloroprocaine epidural. Reg Anaesth 9:124–134, 1984
17. Barsa J, Batra M, Find BR, Sumi M: A comparative in-vivo study of local neurotoxicity of lidocaine, bupivacaine, 2-chloropro-

† Carpenter RL, Morell RC: Bupivacaine and lidocaine are more potent vasodilators than mepivacaine: Effects determined by anesthetic concentration (abstract). ANESTHESIOLOGY 69:A873, 1988.

caine, and a mixture of 2-chloroprocaine and bupivacaine. Anesth Analg 61:961–967, 1982

18. Johns RA, DiFazio CA, Longnecker DE: Lidocaine constricts or dilates rat arterioles in a dose-dependent manner. ANESTHESIOLOGY 62:141–144, 1985
19. Johns RA, Seyde WC, DiFazio CA, Longnecker DE: Dose-dependent effects of bupivacaine on rat muscle arterioles. ANESTHESIOLOGY 65:186–191, 1986
20. Nelson SH, Steinsland OS: Variable effects of lidocaine, mepivacaine and bupivacaine on neurovascular transmission. ANESTHESIOLOGY 69:A140, 1988
21. Rundquist I, Smith QR, Michel ME, Ask P, Oberg PA, Rapoport SI: Sciatic nerve blood flow measured by laser doppler flowmetry and [^{14}C]iodoantipyrine. Am J Physiol 248:H311–H317, 1985
22. Shephard AP, Riedel GL, Kiel JK, Haumschild DJ, Maxwell LC: Evaluation of an infrared laser-Doppler blood flowmeter. Am J Physiol 251:H1211–H1216, 1986
23. Braid DP, Scott DB: The systemic absorption of local analgesic drugs. Br J Anaesth 37:394–404, 1965
24. Tucker GT, Moore DC, Bridenbaugh PO, Bridenbaugh LD: Systemic absorption of mepivacaine in commonly used regional procedures. ANESTHESIOLOGY 37:277–287, 1972
25. Bonica JJ, Akamatsu TJ, Berges PU, Morikawa K, Kennedy WF: Circulatory effects of peridural block: II. Effects of epinephrine. ANESTHESIOLOGY 34:514–522, 1971
26. Sugimoto H, Monafo WW, Shimazaki S: Regional sciatic nerve blood flow response to limb movement. Am J Physiol 252: H439–H441, 1987
27. Monafo WW, Eliasson SG, Shimazaki S, Sugimoto H: Regional blood flow in resting and stimulated sciatic nerve of diabetic rats. Exp Neurol 99:607–614, 1988
28. Meisheri KD, Van Breemen C: Effects of β-adrenergic stimulation on calcium movements in rabbit aortic smooth muscle: Relationship with cyclic AMP. J Physiol (Lond) 331:429–441, 1982
29. Aps C, Reynolds R: The effect of concentration on vasoactivity of bupivacaine and lignocaine. Br J Anaesth 48:1171–1174, 1976
30. Kozody R, Palahnuik RJ, Biehl DR: Spinal blood flow following subarachnoid lidocaine. Can Anaesth Soc J 32:472–478, 1985
31. Kozody R, Palahnuik RJ, Cumming MO: Spinal blood flow following subarachnoid tetracaine. Can Anaesth Soc J 32:23–29, 1985
32. Kozody R, Ong B, Palahniuk RJ, Wade JG, Cumming MO: Subarachnoid bupivacaine decreases spinal cord blood flow in dogs. Can Anaesth Soc J 32:216–222, 1985