

Interpleural Anesthetics in the Dog: Differential Somatic Neural Blockade

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Differential somatic neural effects of interpleural bupivacaine were determined in dogs. Alterations in evoked responses were used as a marker of neural blockade. Electrode pairs were fastened to the external surface of the right seventh ribs of five male mongrel dogs (25–30 kg) at distal (D), middle (M), and proximal (P) locations. Electrodes were similarly fastened to the ipsilateral laminae of the fifth (T5L), seventh (T7L), and ninth (T9L) thoracic vertebrae, and the contralateral cranium over the sensorimotor cortex (SMC). Pediatric feeding tubes were used as interpleural catheters. Following interpleural bupivacaine (10 ml, 0.5%) intercostal nerve block was produced, as manifested by decreases in amplitude (range 12–32% of control, $P < 0.05$), and increases in latency (range 108–126% of control, $P < 0.05$), of evoked potentials recorded between T7L and rib electrodes. The block was found to localize over dependent portions of the rib with changes in animal position, indicating a strong influence of gravity. No significant changes were seen in potentials recorded between T9L and T5L, and T9L and SMC, regardless of position. T9L-T5L and T9L-SMC potentials were abolished or severely attenuated following direct subarachnoid or epidural injection of bupivacaine at T7. Thus, there are no spinal, epidural, or gross CNS effects of interpleural bupivacaine. (Key words: Anesthetic techniques: interpleural. Anesthetics, local: bupivacaine. Monitoring: evoked potentials. Pain: postoperative.)

INTERPLEURAL ADMINISTRATION of local anesthetics for pain management is a recently developed technique.¹ In practice, a catheter is introduced percutaneously between the visceral and parietal pleura and injected with local anesthetic as needed for analgesia. The technique has been effectively employed in a variety of clinical applications. These include postoperative pain relief following incision through the thoracic dermatomes (*e.g.*, cholecystectomy),^{1–5} posttraumatic thoracic pain (*e.g.*, rib fracture and/or flail chest),⁶ and pain management of chronic pancreatitis^{7,8} and herpes zoster.⁸ The site of somatic neural blockade is presumed to be the intercostal nerves as they course proximally beneath the corresponding rib and overlying parietal pleura. Other possibilities include local pleural nerve endings, paravertebral nerve block, and spinal or epidural nerve block. Case reports of efficacy in pancreatic pain,⁷ and of associated Horner's

syndrome,⁹ suggest a component of visceral neural blockade. This might involve splanchnic nerves, sympathetic chain ganglia, or other visceral neural structures.

Somatosensory evoked potential technology has been effectively employed to study the sites of action of epidurally administered local anesthetics.¹⁰ Specifically, decreases in amplitude and increases in latency of evoked responses following the administration of local anesthetic are taken to be the functional equivalent of neural blockade. For the present investigation, we developed a chronic preparation in dogs that allowed for the study of differential somatic neural effects, utilizing alterations in evoked responses as a marker of neural blockade. The purpose in employing such a preparation was to more precisely locate the site or sites of neural blockade following interpleural administration of bupivacaine.

Materials and Methods

MODEL PREPARATION

The study was approved by the Institutional Animal Care and Use Committee. Five adult male mongrel dogs (25–30 kg) were anesthetized with thiamylal and the tracheas were intubated. Anesthesia was maintained with halothane, nitrous oxide, and oxygen *via* mechanical ventilation. Under sterile conditions, chronic femoral arterial and venous catheters were surgically inserted. The external surface of the right seventh rib was exposed and three pediatric gold-plated silver EEG electrode pairs were fastened to it with stainless steel screws and epoxy. Within an electrode pair, the interelectrode distance was 5–8 mm. The distance between electrode pairs was 5–6 cm. Distal electrodes (D) were placed at the costochondral junction and proximal electrodes (P) as close to the costovertebral articulation as possible. Middle electrodes (M) were placed at the midpoint of the distance between the distal and proximal electrodes. Electrodes were similarly fastened *via* posterior midline incision to the ipsilateral vertebral laminae of the fifth (T5L), seventh (T7L), and ninth (T9L) thoracic vertebrae. An electrode pair was also fastened to the cranium overlying the contralateral sensorimotor cerebral cortex (SMC) (fig. 1). The interpleural catheter (10-Fr pediatric feeding tube) was inserted 3–4 cm into the chest with direct vision over the rib. This was done *via* a 3-mm incision in the intercostal musculature and parietal pleura. At no time during the surgical preparation was the pleura incised except for this small entry site of

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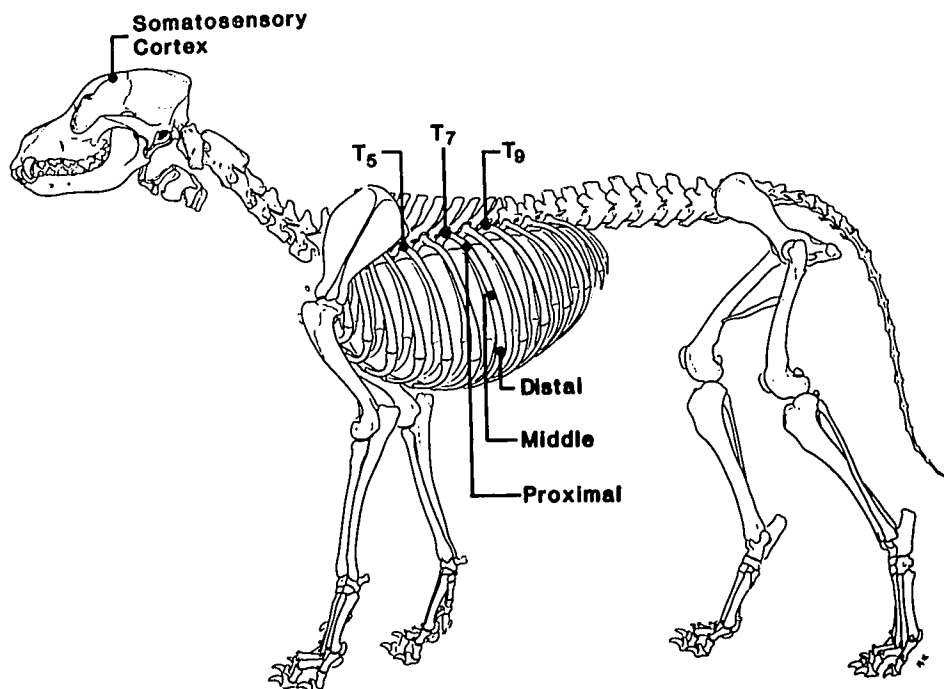


FIG. 1. Electrode location on the canine skeleton. Rib electrodes monitored intercostal nerves. Laminar electrodes monitored spinal cord. Cranial electrodes monitored cerebral cortex. (Modified from Evans HE, Christensen GC: Miller's Anatomy of the Dog, 2nd edition. Philadelphia, WB Saunders, 1979, p 108, with permission.)

the interpleural catheter. Four to five days were allowed for surgical recovery before study.

EXPERIMENTAL PROTOCOLS

On the days of study, the dogs were anesthetized with thiamylal (8 mg/kg) and the tracheas were intubated. Anesthesia was maintained with halothane 0.8% end-tidal concentration, 50% nitrous oxide, and 50% oxygen. Muscle relaxation was facilitated with pancuronium as needed, and the lungs were mechanically ventilated to an end-tidal carbon dioxide of 32–38 mmHg. Throughout the experiments, end-tidal CO₂ and halothane, and inspired N₂O and O₂ were monitored (DATEX gas monitor) and maintained constant. In addition, rectal temperature (38–40° C) and arterial blood pressure (MABP, 100 mmHg) were continuously monitored and remained constant.

Using a Tracor 3000 evoked potential monitor, control evoked potentials were recorded over a 1–2-h period following induction of anesthesia. For intercostal nerve evoked potential evaluations, the stimulus was applied at the T7 lamina to reproducibly obtain an evoked potential at the distal, middle, and proximal rib electrodes. In one animal (P–T7L segment only), the stimulus was applied and recorded in the opposite direction. Stimuli were characterized by a duration of 0.2 ms, frequency of 5.5 Hz, intensity of 2–6 mA, and delay of 0.7–1.0 ms; 250 consecutive stimuli were averaged. We employed a sweep time of 5 ms. Filtering was at 1–1,500 Hz. Local spinal

cord transmission was evaluated using potentials recorded in a similar fashion between laminar electrodes at T9 and T5. Proximal spinal cord, subcortical, and cerebral cortical activity was monitored using potentials recorded between the T9 laminar and cranial electrodes. Potentials were again obtained 30–90 min following injection of the interpleural catheter with either 10 ml of 0.9% preservative-free saline or 10 ml of 0.5% bupivacaine. Only one injection of interpleural saline or bupivacaine was made during each experiment. Stimulus characteristics at each electrode were identical to those used in the pre-injection control period. Injections were randomized and made with the dogs in one of three different positions: study side down (interpleural catheter and rib electrodes lowermost in the horizontal plane), supine (interpleural catheter and rib electrodes in the vertical plane), and study side up (interpleural catheter and rib electrodes uppermost in the horizontal plane). We altered the position of the study side to determine the effects of gravity on the block. At least 48 h was allowed for recovery between each experimental injection. Only four dogs were evaluated in the study side up position.

In separate experiments in three animals, 0.5% bupivacaine was injected into the subarachnoid (1 ml) or epidural (3 ml) spaces at the T7 level. The former was accomplished by performing a lumbar puncture at L3–4 (one animal, one observation), or posterior cisterna magna puncture (two animals, two observations each). A catheter was then threaded through the puncture needle to the T7 level. For epidural injection a needle was inserted un-

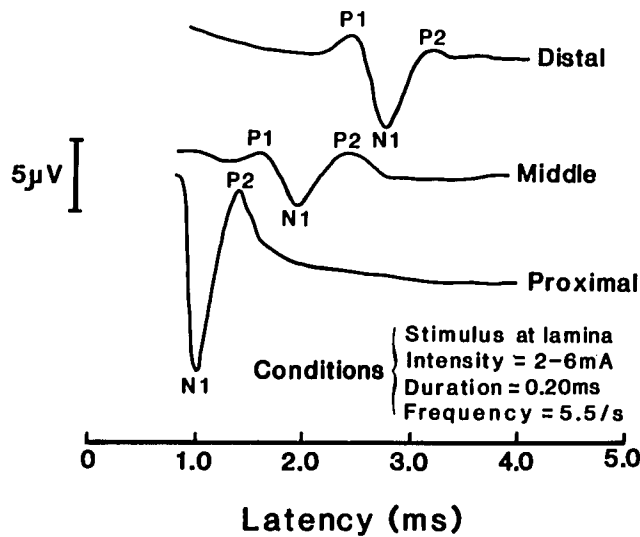


FIG. 2. Representative intercostal nerve evoked potential waveforms recorded in one dog at the distal, middle, and proximal rib electrodes. Stimulus conditions are indicated. There is a progressive increase in latency from the proximal to distal electrodes as the distance the signal travels increases.

der direct vision *via* a posterior midline incision at T7 (one animal, one observation), or a catheter was inserted from the epidural space at the lumbosacral junction (two animals, two observations each). Subarachnoid and epidural catheter tip position at T7 was confirmed by x-ray using contrast materials. T9L-T5L (laminar to laminar) and T9L-SMC (laminar to cortical) potentials were then recorded. Only one epidural or subarachnoid injection was made during each experiment. At least 48 h was allowed for recovery between each experimental injection. These experiments were conducted to confirm the neural effects of directly applied bupivacaine in the subarachnoid or epidural spaces.

For purposes of evoked potential analysis, amplitude (in millivolts) was taken to be the absolute value of the greatest distance from positive to negative peaks (Px-N1) in the recorded potential. Latency was taken to be the elapsed time (in milliseconds) between stimulus and occurrence of the first negative peak (N1 latency). A paired

t test, based on differences, was employed for statistical analysis of control *versus* postdrug potentials. When comparing amplitude and latency results based on animal position (*i.e.*, study side up, study side down, supine), for a given rib segment, a nonparametric Mann-Whitney U test was employed, with a Bonferroni correction for multiple comparisons.

Results

The evoked potentials recorded between T7 laminar and rib electrodes and between different laminar electrodes showed a characteristic pattern of a small positive peak (P1) followed by a deep negative peak (N1) and a second positive peak (P2) (fig. 2). Evoked potentials between laminar and cortical electrodes were identified by the more complex pattern commonly seen with cortical somatosensory potentials. Control amplitude and latency values for evoked potentials recorded over the rib electrodes are presented in table 1. No significant differences were observed when analyzing possible positional effects on amplitudes and latencies for given rib segments.

SALINE CONTROL

Preliminary investigations showed no significant changes in amplitude or latency at any rib, laminar, or cortical electrodes following injection of the interpleural catheter with 10 ml 0.9% preservative-free saline. Amplitudes, expressed as mean per cent of presaline control, ranged from 87.8 to 103.0. Latencies, expressed as mean per cent of presaline control, ranged from 100.5 to 100.8. This excluded any time related effects of the general anesthetic or experimental procedure on evoked potentials in this model over the duration of the study period.

INTERPLEURAL BUPIVACAINE

With the study side down (interpleural catheter and rib electrodes lowermost in the horizontal plane), significant decreases in amplitude (32% of control, $P < 0.05$) were observed only at the distal rib electrode (T7L-D).

TABLE 1. Control Amplitude and Latency Values for Intercostal Nerve Evoked Potentials

	(P _x -N ₁) Amplitude (µV)			(N ₁) Latency (ms)		SS up
	SS down	Supine	SS up	SS down	Supine	
T7L-D	2.56 ± 0.47	5.21 ± 0.27	4.41 ± 1.28	2.45 ± 0.07	2.37 ± 0.04	2.49 ± 0.07
T7L-M	2.81 ± 0.35	4.66 ± 1.53	2.67 ± 0.49	1.70 ± 0.06	1.71 ± 0.04	1.76 ± 0.11
T7L-P	8.94 ± 1.04	15.54 ± 3.24	6.32 ± 0.93	1.07 ± 0.10	1.16 ± 0.05	1.09 ± 0.13
D-M	—	1.87 ± 0.71	—	—	1.41 ± 0.03	—

All values are mean ± SE.

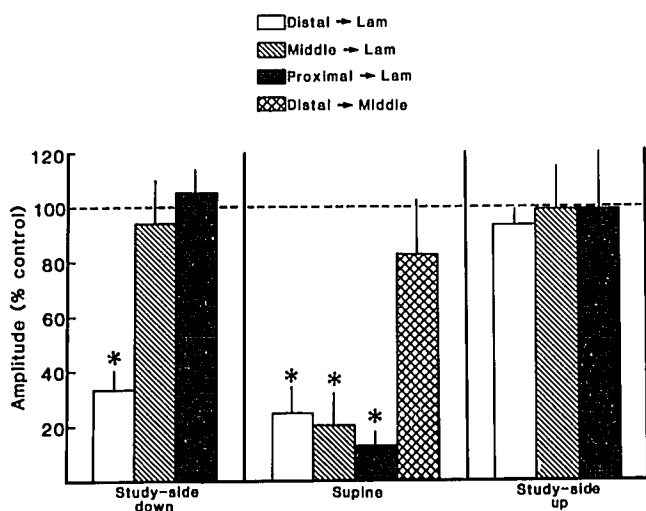


FIG. 3. Segmental intercostal nerve evoked potential amplitudes following interpleural bupivacaine. Data are shown as a function of the position in which the animal was studied. All values are expressed as mean per cent control \pm SE. Control values are in table 1. * $P < 0.05$ versus control.

No significant changes were observed at the middle (T7L-M) and proximal electrodes (T7L-P) (fig. 3). Similar, but not identical, changes in latency expressed as per cent control were observed for the intercostal nerve potentials with the animals in this position. Significant increases in N1 latencies were observed at the distal (T7L-D) and middle (T7L-M) electrodes (126% of control and 108% of control, respectively, $P < 0.05$) but not at the proximal electrode (fig. 4). These results suggest a local anesthetic pooling at the more dependent distal and middle electrodes with the animal in this position. No significant changes in laminar to laminar, or laminar to cortical, amplitudes or latencies were observed, indicating an absence of spinal, epidural, or cortical neural blockade in this position.

With the dogs in the supine position (interpleural catheter and rib electrodes in the vertical plane), significant decreases in amplitude at all rib electrodes (T7L-D, T7L-M, T7L-P) (28% of control, 18% of control, and 12% of control, respectively, $P < 0.05$) were observed (fig. 3). However, amplitudes recorded from the distal to the middle electrode (D-M rib segment) were no different from control. Identical changes in latency were observed in this position. All N1 latencies between the rib and lamina (T7L-D, T7L-M, T7L-P) were significantly increased in this position (114% of control, 122% of control, and 116% of control, respectively, $P < 0.05$) (fig. 4). However, latencies recorded between the more peripheral distal and middle electrode (D-M rib segment) were not different from control (fig. 4). This suggests accumulation of the local anesthetic solution, and thus intercostal nerve block,

at the proximal electrode in this position. No significant changes in laminar to laminar, or laminar to cortical, amplitudes or latencies were observed in this position, indicating an absence of spinal, epidural, or cortical neural blockade.

With the study side up (interpleural catheter and ribs uppermost in the horizontal plane), no significant differences from control amplitudes or latencies were observed at any electrode (T7L-D, T7L-M, T7L-P, T9L-T5L, T9L-SMC), indicating the absence of any somatic neural blockade in this position (figs. 3 and 4).

SPINAL-EPIDURAL BUPIVACAINE

In separate experiments when 1 ml of 0.5% bupivacaine was injected into the subarachnoid space at T7, control potentials T9L-T5L and T9L-SMC were abolished in five of five observations (fig. 5). When 3 ml of 0.5% bupivacaine was injected into the epidural space at T7, control potentials were abolished in three of five observations and severely attenuated in the remaining two observations (amplitude less than 50% control, latency greater than 115% control). This confirms the ability of bupivacaine to alter evoked potentials when allowed access to the spinal or epidural space.

Discussion

The present study, employing a chronic canine model, demonstrates that the interpleural injection of bupivacaine produces intercostal nerve block. The block is manifested by decreases in amplitude and increases in latency of evoked potentials transmitted along intercostal nerves.

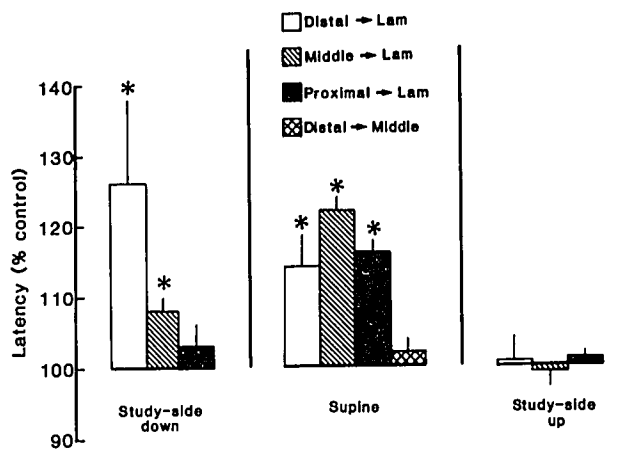


FIG. 4. Segmental intercostal nerve evoked potential N1 latencies following interpleural bupivacaine. Data are shown as a function of the position in which the animal was studied. All values are expressed as mean per cent control \pm SE. Control values are in table 1. * $P < 0.05$ versus control.

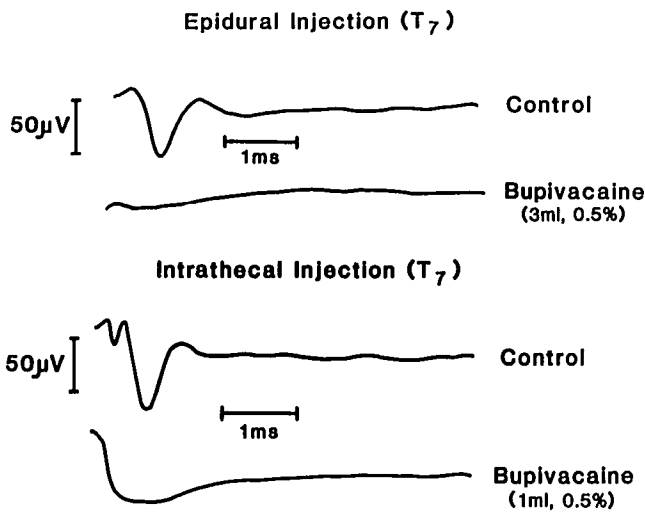


FIG. 5. Representative T9L-T5L evoked potential waveforms before and after subarachnoid or epidural injection of 0.5% bupivacaine at T7. Waveforms were abolished in 5 of 5 subarachnoid injections, 3 of 5 epidural injections, and severely attenuated in 2 of 5 epidural injections following bupivacaine.

We found the distribution of the block to be position-dependent. Because the site of blockade corresponds to the lowermost area of the pleural space in each of the positions studied, it is likely that the distribution of interpleural block is strongly influenced by gravity. These lowermost areas are determined by the position of the thorax in the horizontal and vertical planes.

In the study side down position, significant changes in amplitude and latency were observed at the more dependent distal rib electrode. Significant changes in latency, but not amplitude, were observed at the middle rib electrode. [We are unable to explain this observation. It is generally accepted that amplitude changes occur prior to, or simultaneously with, latency changes.¹¹] However, the latency change at the middle electrode was smaller (108% of control) than that at the distal rib electrode (126% of control), indicating that denser neural blockade occurred distally. No changes in amplitude or latency were seen at the proximal rib electrode. Taken together, these results suggest pooling of local anesthetic solution, and thus intercostal nerve block, at the more peripheral and dependent distal rib electrode in this position (fig. 6). With the animal supine, significant decreases in amplitude and increases in latency were observed at all rib electrodes. The proximal electrode covered the only common segment of intercostal nerve conducting these potentials. These results also suggest pooling of local anesthetic solution, but at the more central and more dependent proximal rib electrodes (fig. 6). Further support for this interpretation is the absence of any evoked potential changes over the

segment of intercostal nerve between the distal and middle electrodes, which is nondependent with the animal supine. With the animal in the study side up position, no changes were observed at any rib electrode. This would be predictable because the mediastinum is dependent in this po-

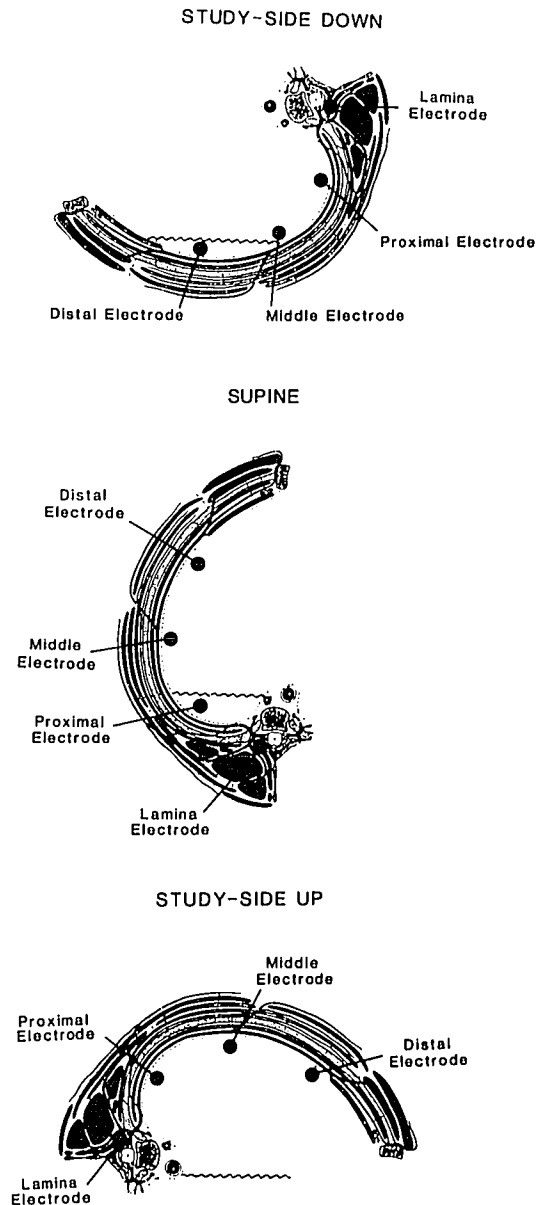


FIG. 6. The seventh rib in each of the three study positions. The wavy lines indicate surface of pool of local anesthetic. The data are consistent with local anesthetic pooling over the distal electrode in the study side down position, over the proximal electrode in the supine position, and over the mediastinum in the study side up position. (Modified from Evans HE, Christensen GC: *Miller's Anatomy of the Dog*, 2nd edition. Philadelphia, WB Saunders, 1979, p 1000, with permission.)

sition, relative to the interpleural catheter and rib electrode (fig. 6). The presence of position-dependent intercostal nerve block in this model of interpleural analgesia is consistent with our own clinical observations and other reports¹² of thoracic dermatomal hypesthesia ipsilateral to the side of interpleural injection of bupivacaine.

There are no spinal or epidural components to the neural changes produced by interpleural bupivacaine in this model. No changes in T9L-T5L or T9L-SMC evoked potentials were observed with the animals in any of the three different study positions. These same laminar to laminar and laminar to cortical potentials were ablated or severely attenuated following direct application of bupivacaine to the subarachnoid or epidural spaces. This demonstrates that bupivacaine does not produce neural blockade at spinal cord structures when injected interpleurally. To our knowledge, there are no clinical reports of bilateral analgesia following unilateral interpleural injection of local anesthetics, a phenomenon that would presumably be mediated by spinal or epidural spread. The preservation of laminar to cortical potentials following interpleural bupivacaine in all three study positions mitigates against gross cerebral effects contributing to interpleural analgesia. This possibility seems remote, given the intensity of the analgesia seen clinically with this technique. Nevertheless, the use of halothane anesthesia during the experiments may have masked subtle alterations in cortical evoked potentials by interpleural bupivacaine.

We chose to study a chronic animal preparation to objectively and reproducibly differentiate the neural effects of interpleural bupivacaine. Evoked potential technology is a widely accepted method of achieving these objectives.^{10,11} Experimental conditions including end-tidal CO₂ and halothane, temperature, blood pressure, and muscle relaxation were held constant throughout the experiments. All of these variables are known to influence evoked potentials.¹¹ No significant changes in amplitude or latency were observed at any electrode following interpleural saline. This ensured that observed changes were drug related and not due to study design or procedures.

A caveat to direct extrapolation of the present results to human patients is interspecies differences in intercostal anatomy when comparing dogs and humans. In humans the parietal pleura is separated from the intercostal nerves by a thin, continuous layer of skeletal muscle known as the intercostalis intimus anterolaterally and the subcostalis posteromedially.⁶ In the dog there is no muscle layer separating the parietal pleura and intercostal nerves.¹³ However, the intercostalis intimus and subcostalis muscles in humans are thin. At their junction over the angle of the rib posteriorly, the parietal pleura is separated from the intercostal nerves by only a thin layer of connective tissue.

It has been proposed that in humans interpleural bupivacaine most readily gains access to intercostal nerves at this site, and later by mass diffusion under or through the intercostalis intimus and subcostalis muscles.¹⁴ This may explain the relatively rapid onset in humans of analgesia following interpleural bupivacaine. We believe the canine thorax, at a minimum, may be considered a widened model of the human thorax. In the dog a lengthy extent of adherent parietal pleura and intercostal nerves occurs in the anterior-posterior dimension.¹³ This facilitated study of block distribution in this axis, parallel to the course of the intercostal nerves. In the study side down position, the block was shown to localize in the more dependent anterior (distal) rib segments. Conversely, in the supine position the block was shown to localize in the more dependent posterior (proximal) rib segments. In humans the longer extent of parietal pleura directly adherent to intercostal nerves occurs in the cephalad-caudad dimension, perpendicular to the course of the intercostal nerves. One might predict that patient positioning in the long axis (head up, supine, head down) would have significant influence on the dermatomal distribution of interpleural analgesia.

The present study design did not allow the specific assessment of any visceral neural effects following interpleural bupivacaine. The possible presence of splanchnic nerve block, block of the sympathetic chain ganglia, or even intraabdominal celiac plexus block in association with interpleural administration of local anesthetics needs to be determined in future studies. They are suggested by the reported efficacy of the technique in pancreatic pain management^{7,8} and case reports of associated unilateral Horner's syndrome.⁹

In summary, interpleural bupivacaine produces intercostal nerve block. The distribution of the block is determined by gravity related pooling of local anesthetic solution in dependent areas of the pleural space. No spinal, epidural, or cerebral neural blockade was demonstrated. The preparation may prove useful in future investigations of the interpleural route of drug administration.

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