

Circulatory Effects of Peridural Block:

II. Effects of Epinephrine

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The influence of epinephrine on the cardiovascular effects of high (T5) peridural analgesia was studied in 19 human volunteers, each of whom received two injections. In 12, the effects of lidocaine alone were compared with those of lidocaine-epinephrine. Peridural analgesia with lidocaine alone produced small (5 to 10 per cent) changes in cardiac output (CO), total peripheral resistance (TPR) and mean arterial pressure (MAP). During peridural analgesia with lidocaine-epinephrine a 49 per cent increase in CO and a 37 per cent decrease in TPR resulted in a 10 per cent decrease in MAP. All of these changes from control were statistically significant and were significantly greater than those produced by lidocaine alone. In another seven subjects, the effects of peridural injection of lidocaine-epinephrine were compared with those of injection of saline-epinephrine. The two solutions produced similar effects on the heart, but lidocaine-epinephrine solution caused a significantly greater decrease in TPR, and consequently in MAP, and a greater increase in leg blood flow than did saline-epinephrine solution. (Key words: Peridural block; Circulatory effects; Lidocaine; Epinephrine; Local anesthetics.)

IN PREVIOUS STUDIES^{1,2} we found that the circulatory responses of a group of human volunteers subjected to high (T5) peridural block

with 2 per cent lidocaine differed significantly from those of other volunteers who received blocks with 2 per cent lidocaine containing 1:200,000 epinephrine. We attributed the difference to the beta-adrenergic stimulating effect of epinephrine. The objectives of the present study were: a) to obtain additional data under more precise conditions by using each volunteer as his own control; b) to define the circulatory effects of epinephrine *per se* after peridural injection; c) to obtain more detailed data on the onset and duration of these circulatory effects.

Methods

Nineteen healthy male volunteers 21 to 42 years of age were studied. Before the study each subject was examined and informed about the nature and risk of the proposed investigation and a written consent obtained. At the time the study was begun, the subjects had fasted for eight hours and were unmedicated. The studies were performed with each subject lying supine in a quiet room. Intravenous infusion of 5 per cent glucose in Ringer's lactate solution was started. With the subject under local anesthesia catheters were inserted percutaneously into the brachial artery and the basilic vein and advanced into the subclavian artery and superior vena cava, respectively. The catheters were connected to strain gauges and a Gilson recorder. A vinyl catheter was inserted into the peridural space with its tip at the level of the second lumbar vertebra. Following a 30-minute rest period, control measurements were made.

In 12 subjects, after control measurements were completed, 18-22 ml of local anesthetic were injected into the peridural space at a rate of 0.5 ml/sec. The dose was estimated on the basis of the age and height of the subject and was intended to achieve analgesia to T5.³

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Five minutes after the injection, cutaneous analgesia was evaluated using firm pin-prick stimulation: testing was repeated every two minutes until analgesia reached the T5 dermatome level bilaterally. Serial measurements were then made and repeated at 30-minute intervals after the injection until all evidence of block had disappeared. During this time, the level of analgesia was determined about every five minutes. A decrease in the level of analgesia two or more dermatomes was considered the end of "therapeutic block," whereas the disappearance of hypalgesia was considered the end of "residual block." Then the subject was given another 30-minute period of rest, new control measurements were completed, a second peridural injection using the same volume of solution was given, and measurements were made at the same intervals as above. Six individuals received only lidocaine in the first injection, and the second injection contained lidocaine with epinephrine 1:200,000; for the other six, the order of the solutions was reversed.

Variables measured continuously were arterial blood pressure (ABP), central venous pressure (CVP), heart rate (HR) and electrocardiogram (ECG); serial measurements of cardiac output (CO), mean arterial pressure (MAP), and arterial blood gases were made. Cardiac output was determined by the indicator-dilution technique using indocyanine green. The area under the dye curve was measured planimetrically with less than 2 per cent mean error in CO determination.⁴ Arterial blood was sampled anaerobically for determinations of P_{O_2} , P_{CO_2} , and pH. Stroke volume (SV) was determined from CO and HR. Total peripheral resistance (TPR) was calculated by the formula:

$$\begin{aligned} \text{TPR units (dynes/sec/cm}^{-5}\text{)} \\ = \frac{\text{MAP (mm Hg)}}{\text{CO (ml/sec)}} \times 1,332 \end{aligned}$$

Left ventricular minute work (LVMW) was calculated by the formula:

$$\text{CO} \times \text{MAP} \times 0.0144 \text{ (kg/m/min)}$$

Left ventricular stroke work (LVSWS) was calculated as:

$$\text{SV} \times \text{MAP} \times 0.0135 \text{ (g-meters)}$$

After the appropriate rest period and control measurements, each of the seven subjects who participated in the second phase received 20 ml of 2 per cent lidocaine-epinephrine (1:200,000), and measurements were made at 5, 15, 30, and 60 minutes. About three hours after complete disappearance of residual peridural hypalgesia, a second set of control measurements was made; then, 20 ml of saline solution containing epinephrine (1:200,000) were injected into the peridural space. For the first half hour after the saline-epinephrine injection, circulatory measurements were made at five-minute intervals to define more precisely the time course of the circulatory effects of peridurally-injected epinephrine during the period when these effects are maximal. In this group the same variables were measured as in the first group but, in addition, limb blood flow was measured by venous plethysmography with Whitney gauges.⁵

Each study consumed seven to ten hours, during which time the subjects received 500–700 ml of fluids. The data were then converted to per cent changes from control values and the significances of the changes were determined with the paired *t* test. The significances of the differences between the means with the two solutions were determined with the unpaired *t* test.

Results

LIDOCAINE AND LIDOCAINE-EPINEPHRINE SERIES

The mean durations and extents of the blocks are shown in figure 1 and the data presented in table 1. Analgesia to T5 was achieved in every subject within 13–20 minutes of injection, and for the ensuing 30–45 minutes it remained within one dermatome of this level except in one subject in whom it reached T2. In each subject the second injection produced an initial level of analgesia which was within one dermatome of that produced by the first injection. Differences between the times of onset of analgesia to T5 (latency) with the two solutions were not significant, but the differences between durations of therapeutic blocks and residual blocks were highly significant.

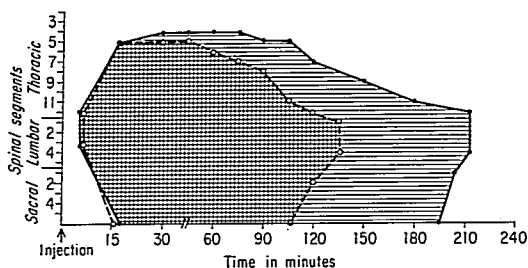


FIG. 1. The mean segments-time profiles (patterns) of peridural analgesia achieved in 12 subjects with 2 per cent lidocaine alone (hatched area) and with 2 per cent lidocaine containing epinephrine 1:200,000 (striped area). Analgesia developed first and persisted longest in segments adjacent to the site of injection.

The circulatory and blood gas changes seen during high peridural analgesia are summarized in figures 2 and 3. Comparison of figures 1 and 2 shows a relation between the duration and pattern (extent) of analgesia and the duration and magnitude of the circulatory changes. Peridural analgesia achieved with lidocaine alone produced maximum circulatory changes during the first 30 minutes after the onset of T5 block. The average changes included an 11 per cent increase in HR and a 5 per cent decrease in SV, which combined to produce a 6 per cent increase in CO. The increase in CO, together with a 10 per cent decrease in TPR, resulted in a 5 per cent decrease in MAP. CVP, LVSW, and LVMW remained very near control values. Only the changes in HR, SV, and TPR were statistically

significant. By 60 minutes after injection, these changes were less than half their peak values, and at 90 minutes, when analgesia had receded to T8 or below, virtually all variables had returned to control values.

Peridural block achieved with lidocaine-epinephrine solution was accompanied by much greater alterations in hemodynamics. Maximal changes, which also occurred during the first 30 minutes of the block, included increases of about 32 per cent in SV, 15 per cent in HR, 49 per cent in CO, 21 per cent in LVSW and 39 per cent in LVMW. These cardiac effects and a 37 per cent decrease in TPR resulted in a 9.8 per cent decrease in MAP. All of these changes from control were statistically significant. By 60 minutes after injection, when analgesia was still at T5, all variables except MAP and CVP had declined to 40 to 50 per cent of their values at 30 minutes, but they were still significantly different from the control values and they remained so for the next hour or more. The differences between the changes produced by lidocaine-epinephrine analgesia and those produced by lidocaine block were statistically significant, except for the changes in CVP.

Continuous arterial blood pressure tracings for each subject were examined to ascertain the effects of peridural analgesia with the two local anesthetic solutions on various components of the arterial blood pressure. Average values of systolic (SBP), diastolic (DBP), pulse (PP), and MAP were calculated at 2½-minute intervals during the first 15 minutes and every 15 minutes thereafter. For simplicity and clarity,

TABLE 1. Latency and Duration of Peridural Analgesia

Event	Lidocaine (Min)	Lidocaine-Epinephrine (Min)
Latency Mean±SD Range	16.1±1.8 13-19	17.2±2.5 13-20
Duration of therapeutic block Mean±SD Range	74 ±10.2 55-90	116 ±20.7* 80-150
Duration of residual block Mean±SD Range	137 ±20.5 100-180	212 ±16.8* 175-235

* $P < 0.01$.

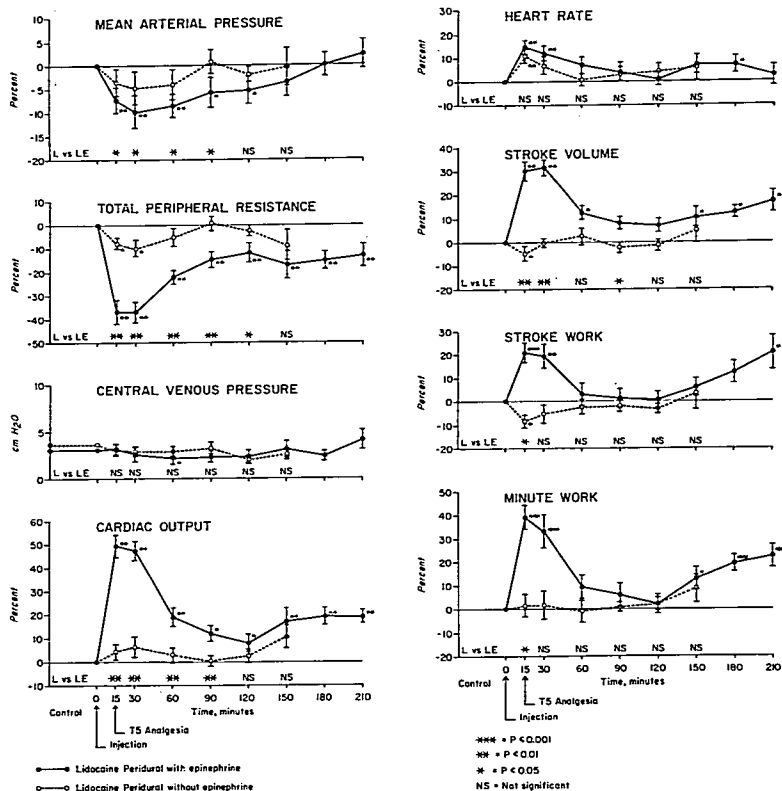


FIG. 2. The circulatory responses to peridural analgesia achieved with 2 per cent lidocaine (O—O) and with 2 per cent lidocaine with epinephrine 1:200,000 (●—●). The value at each time period represents the mean per cent change from mean control value and standard error of the mean for 12 subjects. The values at T5 represent the mean per cent change from control measured when analgesia reached the fifth thoracic dermatome. Statistical significances of the changes from control for each solution are indicated next to the mean values on the graph and the statistical significances between lidocaine (L) and lidocaine-epinephrine (LE) are shown on the bottom of each graph.

figure 3 depicts these average values at less frequent intervals for the first 90 minutes. The effects of lidocaine and lidocaine-epinephrine on blood pressure obviously are significantly different.

The blood gases remained within normal

limits throughout the study with both solutions. The maximum changes seen with lidocaine-epinephrine were: PaO_2 from 90.8 to 93.7 mm Hg; $PaCO_2$ from 35.2 to 37.4 mm Hg; pH from 7.40 to 7.38. Similar small changes occurred with lidocaine alone.

LIDOCAINE-EPINEPHRINE AND SALINE-EPINEPHRINE SERIES

The circulatory responses and arterial blood gases following peridural injection of lidocaine-epinephrine solution and saline-epinephrine solution are summarized in figure 4. Analgesia to T5 developed about 17 minutes after the injection. The residual hypalgesia following peridural injection of lidocaine-epinephrine lasted more than three hours. However, data obtained after 60 minutes are not presented, for simplicity and because we were primarily interested in comparing the effects of the two solutions during their peak circulatory actions. The only significant differences between the lidocaine-epinephrine and the saline-epinephrine solutions occurred in the peripheral vascular bed. Lidocaine-epinephrine solution caused a significantly greater decrease in TPR, and consequently also in MAP, and a greater increase in leg blood flow than did the saline-epinephrine solution.

In this group the blood gases also remained within normal limits with both solutions. Maximum changes seen with lidocaine-epinephrine were: P_{aO_2} from 91.7 to 95 mm Hg; P_{aCO_2} from 38.1 to 37.4 mm Hg; pH from 7.39 to 7.36; base excess from -1.8 to -2.7. Similar changes occurred with saline-epinephrine.

Discussion

It is now well established that the circulatory effects of peridural block are determined not only by the extent of the sympathetic interruption but also by direct action of lidocaine and epinephrine when this is added to the local anesthetic solution and, most importantly, by the condition of the patient.^{7,8,6} In normal man, analgesia extending to T4-5 produced by lidocaine alone is associated with small (5-10 per cent) decreases in MAP and no changes in CO. Apparently the slow onset of block permits effective mobilization of homeostatic mechanisms to compensate for the extensive vasomotor blockade. In amounts usually injected for single-dose block, lidocaine has no apparent circulatory effects, but with accumulation consequent to repeated injections during "continuous" block moderate blood levels which usually produce cardiac stimulation develop, while very high blood levels consequent to accidental intravenous injection of large amounts cause cardiovascular depression.⁶

Our data demonstrate that when epinephrine is incorporated into the local anesthetic solution it plays a major role in determining the cardiovascular effects of peridural analgesia. With the amounts used in this study (80 to 120 μ g) epinephrine produced a predominant beta-adrenergic stimulation. The epinephrine-induced increases in HR, SV, and CO were more than offset by the marked decrease in TPR, resulting in a decrease in MAP. The decrease in MAP and other circulatory changes were significantly greater during peridural analgesia with lidocaine-epinephrine than with lidocaine alone. These data confirm the results of earlier studies,^{7,2} which apparently have not been accurately interpreted by some authors.^{3,7,8} In citing our reports, one writer stated that epinephrine increased blood pressure,³ while others believed that it reduces the incidence of hypotension.^{7,8} In view of this confusion, and because the magnitude and duration of the circulatory effects of epinephrine added to local anesthetics are not widely appreciated, it may be useful to review them.

It is well known that epinephrine stimulates both alpha- and beta-adrenergic receptors.^{9,10} Stimulation of alpha receptors, which are present in all blood vessels, produces vasoconstriction, resulting in increases in TPR and venous return to the heart.^{3,10,11} Stimulation of beta receptors, present in the heart and in vessels of skeletal muscles and in superior mesenteric and splenic arteries,^{11,12} produces increases in SV, HR, and CO, and concomitant vasodilation and decrease in TPR. The net effect of epinephrine on blood pressure depends upon which of the two receptor systems predominates. This, in turn, is influenced by the plasma level of epinephrine, which depends on the mode of administration and dose injected.⁶ Very low levels stimulate only the beta receptors, which are sensitive to much lower concentrations of epinephrine than are the alpha

* A predominant beta response occurs during infusion of epinephrine at rates of less than 0.15 μ g/kg/min¹² or after injection of a single dose of 200-1,000 μ g of epinephrine subcutaneously or intramuscularly¹⁰ and after injection of local anesthetic containing 25-400 μ g of epinephrine for brachial plexus block.^{13,14} An alpha response is seen during intravenous infusion at rates in excess of 0.2-0.3 μ g/kg/min^{10,12} or after intravenous injection of a single dose of 20 μ g or more of epinephrine or following accidental extravascular injection of toxic amounts of epinephrine.

ARTERIAL BLOOD PRESSURE

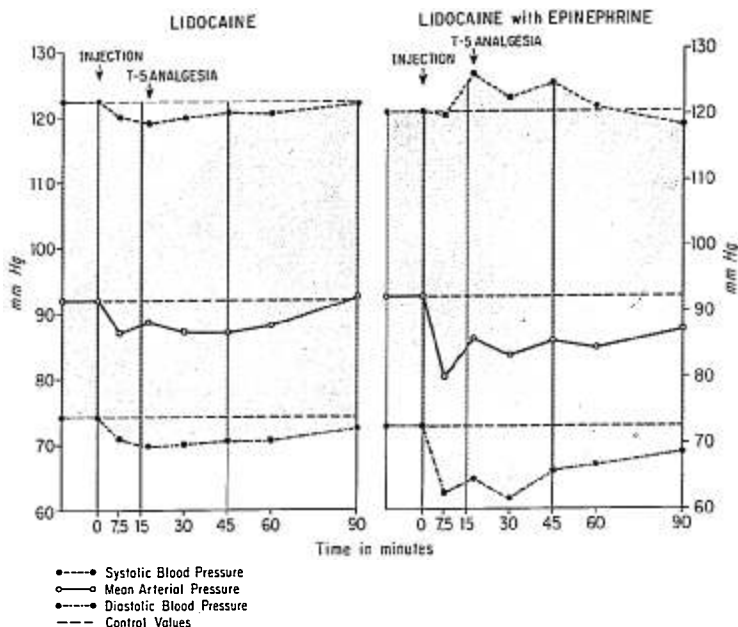
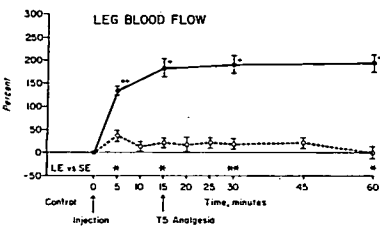
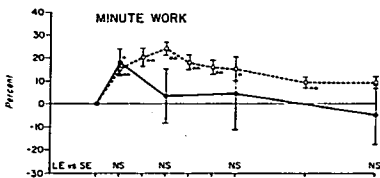
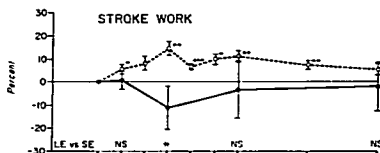
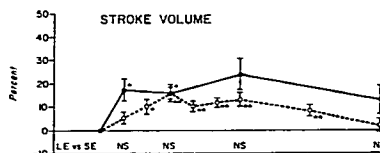
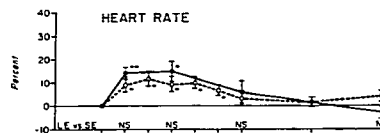
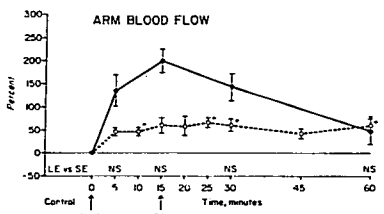
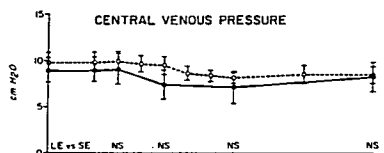
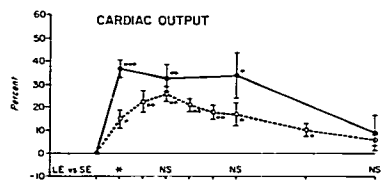
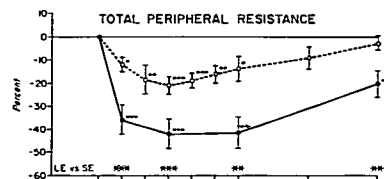
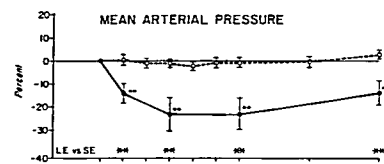


FIG. 3. The mean per cent changes from control mean values in the blood pressures of 12 subjects during the first 90 minutes following peridural injection of 2 per cent lidocaine and 2 per cent lidocaine-epinephrine solution. Peridural analgesia with lidocaine alone produced decreases in SBP (upper line), DBP (lower line) and MAP (middle line), which were of similar magnitude, so that PP remained essentially normal. Lidocaine-epinephrine solution produced greater decreases in DBP and MAP, but a transient increase in SBP, thus markedly increasing PP. Note that the changes in DBP and MAP occurred during the first 7½ minutes, whereas the changes in systolic pressure occurred later.

receptors of the arterial vessels.^{10, 11} Low concentrations of epinephrine also stimulate alpha receptors in veins, increasing the venous return to the heart.^{5, 11} Increases in SV, HR, CO, and SBP are offset by decreases in DBP and TPR, resulting in either no change or a small decrease in MAP.^{10, 12} In vessels deprived of sympathetic nerves by surgical sympathectomy, the beta-adrenergic stimulating action of epinephrine is enhanced.¹⁴

Following injection of a local anesthetic solution containing epinephrine into the peridural space, epinephrine is absorbed very

slowly, owing to its local vasoconstrictor action. Consequently, blood levels of epinephrine achieved produce a predominant beta-adrenergic stimulation. This action on beta receptors combines with the vasomotor blockade associated with peridural analgesia to produce a significantly greater decrease in TPR than that produced by either vasomotor block or epinephrine alone. Consequently, despite the significant increases in CO and SBP produced by epinephrine, DBP and MAP are decreased more than if epinephrine is omitted from the local anesthetic.



●—● Lidocaine Peridural with Epinephrine
○—○ Saline Peridural with Epinephrine

*** = P < 0.001
** = P < 0.01
* = P < 0.05
NS = Not significant

Fig. 4. The circulatory response to peridural injection of 20 ml of 2 per cent lidocaine with epinephrine 1:200,000 (●—●) and to peridural injection of the same volume of saline-epinephrine (○—○). The value at each time period represents the mean and standard error of the mean for seven subjects. The values at T5 represent the mean per cent change from control measured when analgesia reached the fifth thoracic dermatome. Statistical significances of the changes from control for each solution are indicated next to the mean values on the graph and the statistical significances between lidocaine-epinephrine (LE) and saline-epinephrine (SE) are shown on the bottom of each graph.

The cardiovascular effects of epinephrine injected into the peridural space appear in 3–5 minutes and in 10–15 minutes achieve maximum values, which are maintained for 15–30 minutes and then decay during the ensuing 30 minutes and disappear in 90–120 minutes. These results, along with those of other studies,^{15–17} indicate that the degree and duration of beta-adrenergic response are directly related to the amount of epinephrine injected. In subjects given peridural injections of lidocaine containing different amounts of epinephrine, TPR values decreased a maximum of approximately 20 per cent with 50 µg, 40 per cent with 100 µg, 50 per cent with 150 µg, and nearly 65 per cent with 300 µg, whereas CO values increased 20, 40, 55, and 70 per cent, respectively.¹⁷ The durations of major circulatory changes were approximately 30, 55, 70, and 105 minutes, respectively, with the changes in TPR lasting about 10–30 minutes longer than those in CO.

Our data on the duration of the circulatory effects of epinephrine differ from the generally-held opinion recently expressed by Bromage,³ who stated that they last only 5–10 minutes. This general belief in the short action of epinephrine probably evolved from the fact that when the drug is given intravenously its action is quickly terminated by rapid clearance from blood by the heart and other organs innervated by adrenergic fibers.¹⁵ Several factors probably contribute to its prolonged circulatory effects following peridural injection. First, because of its local vasoconstricting action, all of the epinephrine is not absorbed from the peridural space into the circulation for some time. Although no data on plasma levels of epinephrine following peridural injection are available, indirect evidence suggests that the drug produces local vasoconstriction for 30–90 minutes, depending on the concen-

tration and total dose.^{15, 19} Second, since the biotransformation of epinephrine by catechol-o-methyltransferase in the plasma is a slow process,²⁰ the amount of epinephrine biotransformed in the peridural space is probably insignificant. On the basis of these considerations and our data, one may speculate that exogenous epinephrine is present in the blood for 60–120 minutes, depending on the total amount administered. This issue is being studied in our laboratory.

Our data suggest that the action of epinephrine on peripheral vessels begins a few minutes before, and persists after, that on the heart. Moreover, there seems to be a synergistic action between epinephrine and vasomotor blockade. Thus, it is noted that the decrease in TPR was 50 per cent greater with peridural analgesia produced with lidocaine-epinephrine than the added decrease in TPR caused by epinephrine and vasomotor block achieved with lidocaine alone. The prolonged decrease in TPR probably resulted from a persistent vasomotor block in the lower limbs and pelvis. Daos and Virtue²¹ found that after peridural anesthesia with 1.5 per cent lidocaine containing 1:200,000 epinephrine, blocks of sympathetic function persisted an average of 45 minutes longer than peridural analgesia. Since the preganglionic neurons supplying the lower limbs and pelvis are within T10–L2 segments,²² and since in our volunteers analgesia of these segments persisted for more than 150 minutes, it may be presumed that vasomotor block persisted for three hours.

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Drugs

MUSCLE RELAXANT ACTION The classical experiments of Claude Bernard established that curare acted at the myoneural junction. Langley, in 1905, and Dale and associates, in 1936, postulated that the drug acted by occupying cholinergic receptor sites on the postjunctional membrane. In recent years, Hubbard and other workers have suggested that the presynaptic effects of muscle relaxants may be of major importance. Paton and Zaimis, in 1952, proposed that neuromuscular blockade resulted from competition between acetylcholine and curare-like drugs for the receptor sites. This theory was elaborated in 1961 by Paton, who proposed that the point of equilibrium in such a dynamic state would depend upon the rate of reaction between the drug and the receptor. If the competition theory is correct, it must fulfill certain criteria: 1) the equilibrium-dose ratio between the agonist, in this case acetylcholine, and the antagonist, a curare-like drug, must be a constant; 2) the rate of association and dissociation of a drug with a receptor site must be of the same order if the amount of entropy in the system is constant. It has always been assumed that the degree of paralysis produced by a drug is dependent upon the blood, and hence the extracellular fluid (ECF), level of the agent, and that lowering the blood and ECF concentrations would, therefore, reverse the paralysis. The present work suggests that this assumption is not valid for anesthetized human patients. (Feldman, S. A., and Tyrrell, M. E.: *A New Theory of the Termination of Action of the Muscle Relaxants*, *Proc. Roy. Soc. Med.* 63: 692 (July) 1970.)