The effect of subarachnoid epinephrine and phenylephrine on spinal cord blood flow

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Eighteen mongrel dogs were divided into three equal groups. Spinal cord and spinal dural blood flow in the cervical, thoracic and lumbosacral regions were measured using the radioactive microsphere technique. Measurements were taken before and 10 and 40 minutes after lumbar subarachnoid injection of one of the following: (1) physiologic saline: (2) epinephrine 200 µg or (3) phenylephrine 5 mg. No significant change in spinal cord blood flow occurred in any of the groups, nor was there any difference between the groups. Dogs receiving subarachnoid phenylephrine did demonstrate a significant reduction of thoracic dural blood flow at ten minutes. Dogs receiving intrathecal epinephrine or phenylephrine demonstrated a significant reduction in lumbo-sacral dural blood flow at ten minutes after injection. The reduction in dural blood flow was still evident at 40 minutes in dogs receiving phenylephrine. Subarachnoid epinephrine (200 µg) and phenylephrine (5 mg) do not effect spinal cord blood flow but do produce regional dural vasoconstriction.

Key words

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Since the clinical introduction of epinephrine as an adjunct in prolonging spinal anaesthesia by Braun[1] in 1900, anaesthetists have questioned its possible role in the production of spinal cord ischaemia. Large prospective and retrospective series using spinal anaesthesia with epinephrine and phenylephrine have demonstrated an extremely low incidence of neurological complications.[2,3] However, the occasional reports of motor abnormalities following spinal anaesthesia with vasoconstrictors nearly always implicate spinal cord ischaemia as a possible mechanism of injury. The concept that vasoconstrictors prolong spinal anaesthesia by inducing spinal cord vasoconstriction is based on several previous studies and an inference from the vasoconstricting effects of epinephrine and phenylephrine on peripheral vascular beds.[4]

Biberfield in 1907[5] reported that intrathecal epinephrine had a vasoconstricting effect on the spinal cord in animals. More recent evidence suggesting a vasoconstricting effect of intrathecal epinephrine came from a study in animals by Usubiaga *et al.*[6] in 1969 in which he reported a decrease in spinal cord blood flow in dogs following intrathecal epinephrine.

Since spinal anaesthesia has become the anaesthetic of choice in many situations, it is important that we know the effects of vasoconstrictors on the spinal circulation. This study was undertaken to determine the effects of subarachnoid epinephrine (200 µg) and phenylephrine (5 mg) on spinal cord blood flow in dogs.

Methods

Eighteen mongrel dogs of both sexes weighing 17–25 kg (22.5 ± 3.2, mean ± SD) were used in the study. They were anaesthetized with pentobar-

bitone, 30 mg·kg^{-1} induction dose, followed by a maintenance dose of 2–5 mg·kg^{-1}·hr^{-1}. After tracheal intubation, the animals were ventilated with 100 per cent oxygen at a tidal volume of 15 ml·kg^{-1}. The respiratory rate was adjusted to maintain a PaCO$_2$ of 35–42 torr.

The surgical preparation was as follows. A right inguinal incision was used for insertion of polyvinyl catheters in the femoral artery and vein. A left inguinal incision was used for the retrograde insertion of a catheter through the femoral artery into the left ventricle. Using continuous pressure monitoring, the disappearance of the aortic diastolic pressure trace signified that the catheter had been placed appropriately in the left ventricle. The position of this catheter was subsequently validated by postmortem examination. A Swan-Ganz thermodilution catheter was inserted using the left jugular vein.

Each animal was allowed to recover for 40 minutes following the cut downs prior to proceeding with the study. The mean arterial blood pressure (MABP), mean pulmonary artery pressure (PAP), and heart rate (HR), were recorded continuously, while cardiac output (CO) and pulmonary capillary wedge pressure (PCWP) were determined prior to each flow determination. CO was measured by the thermodilution of 5 ml of 0.9 per cent saline at room temperature using an Edwards cardiac output computer. Core temperature was continuously measured using the thermistor on the thermodilution catheter. Arterial blood gases (ABG) were measured at 15-minute intervals and immediately prior to each blood flow determination. Blood was drawn from the femoral arterial catheter, analyzed on a Corning Blood Gas Machine, and temperature corrected. No studies were performed unless PaCO$_2$ was 35–42 and pH > 7.32. A pH < 7.32, when present, was corrected with intravenous NaHCO$_3$.

Following the stabilization period, spinal cord and dural arterial blood flow were measured by the radioactive microsphere technique. This method of measuring regional blood flow has been fully described as an accurate and reproducible technique[7–9] and has been extensively used in our laboratories. In short, a suspension of 6–10 × 10^6 microspheres (15 ± 0.5 microns in diameter) labelled with one of cerium[141], chromium[51] or strontium[85] is thoroughly mixed in saline and injected into the left ventricle. Just prior to injection, withdrawal of blood from the femoral artery was started and continued for 30 seconds after completion of the injection into the left ventricle. Radioactive counts in the arterial blood were used as the reference to calculate blood flow to the spinal cord and dura. By comparing microsphere counts trapped in the tissue to counts in the arterial blood supplying that tissue (arterial reference sample), we were able to calculate blood flow to the tissue. Three blood flows to each tissue were measured using the three different radioactive labels on the microspheres.

Following control blood flow measurements, a lumbar dural puncture was performed at the L5–L6 interspace using a 22 gauge spinal needle. Successful dural penetration was demonstrated with the free flow of cerebral spinal fluid from the needle hub. Animals were randomly assigned to receive one of three solutions intrathecally.

(a) Physiologic saline – 5 ml.

(b) Epinephrine 200 μg in physiologic saline – 5 ml.

(c) Phenylephrine 5 mg in physiologic saline – 5 ml.

The solutions were at 20° C and the rate of injection was standardized at 0.5 ml per second. Following intrathecal injection the needle was removed, the dogs were placed supine and the table levelled. Repeat blood flow measurements were performed at 10 and 40 minutes after intrathecal injection.

Following the spinal flow measurements the animals were sacrificed by the intravenous injection of saturated KCl solution. The spinal cord and dura were removed intact, and divided into cervical, thoracic and lumbosacral regions. The dura was dissected from the spinal cord and microsphere counts performed on each cord and dural specimen. Blood flow to the spinal cord and dural areas was measured using the technique described.

All data were analyzed using analysis of variance and Student's paired and unpaired t tests where appropriate. The data are presented as a mean value ± standard error of the mean. A value of p < 0.05 is considered to be significant.

Results

In all groups, MABP, PAP, PCWP were similar and remained constant throughout the study period. In the epinephrine group, cardiac index was moderately elevated at 40 minutes following injection

TABLE I Arterial blood gases, pH and temperature prior to and following intrathecal injection

Groups	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	pH	Temperature (°C)
Saline				
Pre-injection	495 ± 14	38 ± 1	7.35 ± 0.01	38.8 ± 0.3
10 min post-injection	501 ± 4	40 ± 1	7.34 ± 0.01	38.7 ± 0.4
40 min post-injection	484 ± 16	39 ± 1	7.35 ± 0.01	38.6 ± 0.4
Epinephrine				
Pre-injection	508 ± 8	39 ± 1	7.38 ± 0.02	38.5 ± 0.3
10 min post-injection	511 ± 13	39 ± 2	7.38 ± 0.02	38.4 ± 0.3
40 min post-injection	528 ± 15	40 ± 1	7.36 ± 0.01	38.6 ± 0.3
Phenylephrine				
Pre-injection	483 ± 13	40 ± 2	7.35 ± 0.01	38.1 ± 0.1
10 min post-injection	483 ± 13	40 ± 2	7.34 ± 0.01	38.1 ± 0.1
40 min post-injection	501 ± 12	40 ± 1	7.33 ± 0.01	38.0 ± 0.2

n = 6 in each group.
Results are Mean ± S.E.M.
No significant difference.

$(270 \pm 16 \, ml \cdot kg^{-1} \cdot min^{-1}$ compared to control $206 \pm 73 \, ml \cdot kg^{-1} \cdot min^{-1})$. In the phenylephrine group, heart rate fell significantly at 40 min ($117 \pm 8 \, beats \cdot min^{-1}$ compared to control $167 \pm 9 \, beats \cdot min^{-1}$).

ABG, pH and temperature values were similar in the three groups throughout the study (Table I).

TABLE II Spinal cord blood flow prior to and following intrathecal injection

Groups	Cervical cord	Thoracic cord	Lumbo-sacral cord
	Regional flow ($ml \cdot 100 \, gm^{-1} \cdot min^{-1}$)		
Saline			
Pre-injection	23 ± 5	16 ± 3	27 ± 4
10 min post-injection	18 ± 4	14 ± 3	32 ± 5
40 min post-injection	20 ± 4	18 ± 4	39 ± 6
Epinephrine			
Pre-injection	20 ± 6	15 ± 4	24 ± 5
10 min post-injection	19 ± 2	15 ± 1	26 ± 2
40 min post-injection	21 ± 1	18 ± 3	36 ± 4
Phenylephrine			
Pre-injection	16 ± 2	13 ± 3	23 ± 3
10 min post-injection	17 ± 2	12 ± 2	32 ± 5
40 min post-injection	18 ± 2	12 ± 2	37 ± 5

n = 6 in each group.
Results are Mean ± S.E.M.
No significant difference.

Pre-injection measurements of spinal cord blood flow were similar in any given region in the three groups. Dogs receiving intrathecal phenylephrine or epinephrine did not demonstrate a statistically significant change in spinal cord blood flow in any region over time when compared to the preinjection period or to the saline control group (Table II).

In one dog receiving intrathecal epinephrine, myoclonic movements of the hind limbs was noted. This occurred within two minutes of the injection and persisted throughout the 40-minute observation period.

Cervical dural blood flow was similar in the three groups at 10 and 40 min (Table III). Lumbosacral dural blood flow, however, significantly increased at 10 and 40 min following dural puncture and intrathecal saline. In dogs receiving intrathecal neosynephrine a significant decrease in thoracic dural blood flow occurred at ten minutes. In dogs receiving phenylephrine or epinephrine, a significant reduction in blood flow to the lumbosacral dura occurred ten min after injection. The dural vasoconstriction in the lumbosacral region was still evident at 40 minutes in dogs receiving phenylephrine.

Discussion

Autoregulation of spinal cord blood flow has been previously documented. Autoregulation has been

shown to occur between a MABP of 60 to 160 mmHg in dogs.[10] These autoregulatory MABP limits were not exceeded in the present study. PaO_2, $PaCO_2$[11] and temperature[12] have also been shown to be important variables influencing the spinal cord circulation. These parameters were closely controlled in our study.

Intrathecal physiological saline was used as a control because of its lack of effect on sympathetic nerve conduction. Hypotonic solutions may produce a sympathetic blockade by a direct effect on nerve fibres.[13] An injectate volume of 5 ml was chosen to ensure rapid spread in the subarachnoid space.

The microsphere technique is useful in measuring spinal cord blood flow. It does not necessitate a laminectomy or direct spinal cord invasion, both of which may alter spinal cord blood flow.[7,14]

Spinal cord blood flow (SCBF) in the cervical, thoracic and lumbosacral regions in our dogs prior to intrathecal injections are similar to previously published results.[15] Comparison of spinal dural blood flow was not possible as it has not been previously reported. Spinal dural blood flow is relatively low in comparison to other tissues and a large variability might be expected because of low isotope counts. The variability seen in dural blood flow, however, was low.

Cervical, thoracic and lumbosacral spinal cord blood flow were not significantly changed in the three groups studied at 10 and 40 minutes. There was, however, a tendency for lumbosacral spinal cord blood flow to increase in the three groups with time. The specific reason for the increase is not known. Possible mechanisms may be related to dural puncture, barotrauma from the injection, temperature of the injectate or a direct effect of 0.9 per cent saline. While epinephrine and phenylephrine did not affect regional spinal cord blood flow, white and grey matter flows were not differentiated.

Cervical and thoracic dural blood flow remained unchanged in the 0.9 per cent saline group. There was a significant increase in lumbosacral dural blood flow following dural puncture and intrathecal saline. The reasons for the regional dural hyperaemia is also unknown. Mechanisms similar to those suggested to explain the increase in spinal cord blood flow should be considered. Epinephrine and phenylephrine prevented the regional dural

TABLE III   Spinal dural blood flow prior to and following intrathecal injection

| | Regional flow $(ml \cdot 100 \ gm^{-1} \cdot min^{-1})$ | | |
Groups	Cervical dura	Thoracic dura	Lumbo-sacral dura
Saline			
Pre-injection	5.7 ± 1.3	3.7 ± 0.7	4.2 ± 0.9
10 min post-injection	4.2 ± 1.1	6.1 ± 1.4	$9.1 \pm 1.1*$
40 min post-injection	7.5 ± 0.8	6.2 ± 1.4	$7.0 \pm 0.9*$
Epinephrine			
Pre-injection	3.6 ± 0.8	2.6 ± 0.4	3.8 ± 0.7
10 min post-injection	2.8 ± 0.5	2.1 ± 0.5	$1.7 \pm 0.4*$
40 min post-injection	5.6 ± 0.2	3.0 ± 1.1	3.7 ± 0.6
Phenylephrine			
Pre-injection	3.6 ± 0.5	3.8 ± 1.1	4.8 ± 0.8
10 min post-injection	3.8 ± 0.4	$1.8 \pm 0.2*$	$1.4 \pm 0.1*$
40 min post-injection	7.3 ± 1.9	3.0 ± 1.0	$2.2 \pm 0.3*$

$n = 6$ in each group.

Results are Mean $\pm$ S.E.M.

$*p < 0.05$ when compared to pre-injection period.

hyperaemia seen with 0.9 per cent saline. Lumbosacral dural blood flow was significantly decreased following intrathecal epinephrine and phenylephrine at ten minutes postinjection. The response of the dural circulation to vasoconstrictors is similar to that seen in peripheral vascular beds.

The doses of epinephrine (200 µg) and phenylephrine (5 mg) used in the present study are similar to doses recommended for clinical use. Systemic absorption of these agents is the probable explanation for the increase in cardiac index seen with epinephrine and the decrease in HR with phenylephrine in our study.

The decrease in dural blood flow may be partially responsible for the prolonged duration of tetracaine spinal anaesthesia when epinephrine or phenylephrine are used as adjuncts. Since most currently used local anaesthetics with the exception of cocaine, produce vasodilation, the effect of added epinephrine or phenylephrine may be to prevent local anaesthetic induced spinal cord or dural vasodilation. This would affect the absorption of various anesthetics to varying degrees depending on intrinsic vasodilatory activity and lipid solubility. Tetracaine which is extremely lipid soluble will diffuse into biological membranes rapidly. The important factor in the absorption of tetracaine

would, therefore, be the regional blood flow. Agents such as lidocaine and bupivacaine which are less lipid soluble (lidocaine < bupivacaine) will be dependent to a greater degree on rate of diffusion rather than regional blood flow. The effect of rate of diffusion would be maximal when a large surface area for absorption is present, such as in the subarachnoid space.[16]

This hypothesis may explain why epinephrine and phenylephrine prolong the duration of clinically useful tetracaine spinal anaesthesia but not lidocaine or bupivacaine spinal anaesthesia.[17,18] The explanation is consistent with the pharmacokinetic data presented by Denson showing that plasma concentrations of intrathecal lidocaine and the time to reach peak plasma concentrations were identical with and without epinephrine or phenylephrine.[19,20] However, before this issue can be clarified, data concerning the relative vasodilatory effects of the various local anaesthetics on the spinal cord and dural circulation is required.

The addition of epinephrine or phenylephrine to local anaesthetics with a lower lipid solubility (e.g., lidocaine) may produce a prolonged total duration of analgesia through a direct spinal neuronal effect.[21,22]

The contrasting effects of epinephrine and phenylephrine on two differing vascular beds in close proximity (i.e., the spinal cord and dura) have been demonstrated. Our findings suggest that subarachnoid epinephrine and phenylephrine do not produce vasoconstriction of the spinal cord circulation. It is unlikely that this mechanism is responsible for the rare but serious neurologic deficits following spinal anaesthesia. In situations in which neurologic injury occurs consideration should be directed at pre-existent neurological and systemic disorders, traumatic injury and the specific agent and concentration used.

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Résumé

Chez 18 chiens bâtards répartis en trois groupes égaux, le flux sanguin de la moelle épinière et de la duremère a été mesuré dans les régions cervicales, thoraciques et lombosacrées par microsphères radioactives. Les mesures ont été effectuées avant et 10 minutes et 40 minutes après l'injection de l'un des produits suivants: 1) soluté salin, 2) épinéphrine 200 µg, 3) phényléphrine 5 mg. On n'a pas observé de changement notable de la perfusion médullaire dans aucun groupe et aucune différence n'a été observée d'un groupe à l'autre.

Seule la perfusion duremérienne a été modifiée par les injections comme suit: la phényléphrine sous-arachnoïdienne a réduit de façon significative le flux duremérien thoracique dix minutes après l'injection. De même on a observé une réduction significative du flux duremérien lombo-sacré dix minutes après l'injection d'épinéphrine et de phényléphrine; cette diminution du flux duremérien était encore présente 40 minutes après l'injection de phényléphrine. On en conclut que dans ce modèle expérimental, l'épinéphrine sous-arachnoïdienne (200 µg) et la phényléphrine (5 mg) ne modifient pas le flux médullaire mais provoquent une vasoconstriction dans la circulation duremérienne régionale.