

## Blood-Brain Barrier Function Following Drug-induced Hypotension in the Dog

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To examine the effects of hypotension induced either with trimethaphan (TMP) or nitroprusside (NTP) on blood-brain barrier (BBB), penetration of Evans blue (EB) was observed in dogs anesthetized with halothane. Dogs given TMP were divided into two groups: Group 1, seven dogs rendered hypotensive to mean cerebral perfusion pressure (CPP) of 45 mmHg for 45 min and then of 30 mmHg for 45 min; Group 2, three dogs examined 3 days after arterial hypotension identical to that in Group 1. Dogs given NTP were divided into four groups: Group 1, seven dogs rendered hypotensive with NTP (at dose < 1 mg/kg) identical to the TMP-Group 1; Group 2, three dogs examined as the TMP-Group 2; Group 3, seven dogs rendered hypotensive to CPP 45 mmHg for 45 min; Group 4, seven dogs rendered hypotensive with NTP (at dose > 1 mg/kg) identical to the NTP-Group 1. In all dogs, the dorsal cortical surface and standardized serial coronal sections were examined for evidence of EB penetration. The mean EB penetration score ( $\pm$ SEM) for TMP-Groups 1 and 2 was  $12 \pm 6$ ,  $0 \pm 0$ , respectively, and for NTP-Groups 1, 2, 3, and 4 was  $105 \pm 14$ ,  $30 \pm 7$ ,  $6 \pm 6$ , and  $125 \pm 26$ , respectively. These results suggest that dysfunction of the BBB in the NTP group was more pronounced than in the TMP group. (Key words: Anesthetic techniques: hypotension, nitroprusside, trimethaphan. Brain: blood-brain barrier. Sympathetic nervous system: ganglionic blocking agents, trimethaphan. Pharmacology: nitroprusside; trimethaphan.)

TRIMETHAPHAN (TMP) AND NITROPRUSSIDE (NTP) are used widely as hypotensive drugs in anesthesia, and previous reports have shown that cerebral blood flow,<sup>1-3</sup> brain tissue oxygen tension,<sup>4</sup> and neuronal function<sup>5</sup> are maintained better with NTP (at dose levels below 1 mg/kg). The lower cerebral perfusion with TMP might damage the blood-brain barrier (BBB) through ischemia,<sup>6</sup> but, on the other hand, NTP might open the BBB through the mechanism of vasodilation.<sup>7</sup> The integrity of the BBB is important in controlling the movement of fluid, drugs, and hormones into the brain, and so the present study was designed to assess the effect of TMP and NTP hy-

potension on BBB as measured by leakage of the protein-bound dye Evans blue (EB).

### Methods and Materials

Thirty-four mongrel dogs, weighing 8-20 kg, were anesthetized with 2-3% halothane and 60% nitrous oxide in oxygen, followed by succinylcholine 2 mg/kg im, to facilitate endotracheal intubation. Succinylcholine was administered intravenously at  $4 \pm 1$  (SEM)  $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  to maintain muscle paralysis. Ventilation was controlled with a Harvard pump (NSH-34 RH). End-tidal concentrations of carbon dioxide and halothane were monitored by a mass spectrometer (Medspect MS8, Scientific Research Instruments, Maryland) throughout the study. Anesthesia during surgery were maintained with 1-1.5% halothane and 60% nitrous oxide in oxygen. Bilateral catheterization of the femoral arteries and veins was performed for blood sampling, blood pressure monitoring, infusion of Ringer's lactated solution ( $4 \pm 1$  (SEM)  $\text{ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ), and of hypotensive drugs.

With the head supported by a stereotaxic apparatus, the skin and muscle were reflected from the skull and metal screw electrodes for unipolar electroencephalogram (EEG) recording were placed on the dura of the frontal and occipital areas. The electrodes were connected to preamplifiers (Nihon Kohden, AB-620, Tokyo, Japan) for the subsequent recording of the EEG. A 20-gauge needle was inserted into the cisterna magna for the measurement of cerebrospinal fluid pressure (CSFP). After completion of the surgical preparation, nitrous oxide was discontinued and halothane concentration was reduced to  $0.88 \pm 0.03$  (SEM) per cent expired for at least 1 h for stabilization.  $\text{FIO}_2$  was kept constant at 0.4 using nitrogen, and ventilation was adjusted to maintain normocapnia ( $\text{PaCO}_2$ ,  $36 \pm 1$  [SEM] mmHg) throughout the experiment.

Arterial blood pressure and CSFP were measured with a pressure transducer (Nihon Kohden, MP-0.5-290-0-III, Tokyo, Japan), and cerebral perfusion pressure (CPP) was calculated as the difference between mean arterial pressure (MAP) and CSFP, zero reference being at the level of external auditory canal. Arterial blood samples were taken for blood gases and pH analysis, using appropriate electrodes (Instrumentation Laboratory, IL meter 313, Massachusetts). The concentrations of glucose,

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lactate, and pyruvate in arterial blood were determined by enzymatic methods.

After control measurements of pressures, blood gases, hemoglobin, and temperature at 5, 15, and 40 min and of glycolytic metabolites at 15 min before hypotension, TMP dogs randomly were divided into two groups: Group 1—CPP of 45 mmHg for 45 min and then of 30 mmHg for 45 min (seven dogs). Group 2—Animals were evaluated for 3 days after a period of TMP arterial hypotension as in Group 1 (three dogs).

After control measurements identical to that of the TMP dogs, NTP dogs randomly were divided into four groups: Group 1—CPP of 45 mmHg for 45 min and then of 30 mmHg for 45 min with less than 1 mg/kg NTP (*i.e.*, identical CPP to TMP—Group 1) (seven dogs). Group 2—Animals were evaluated for 3 days after a period of NTP arterial hypotension as in Group 1 (three dogs). Group 3—CPP of 45 mmHg for 45 min (seven dogs). Group 4—The same degree of NTP hypotension as Group 1 but using more than 1 mg/kg NTP (seven dogs).

TMP solution was prepared by diluting trimethaphan (Hoffman-La Roche, Switzerland) with 5% glucose solution. NTP was prepared 30 min before infusion by diluting sodium-nitroprusside crystals (Nakarai Chemical, Kyoto, Japan) in 5% glucose solution, which then was protected from light with aluminum foil. TMP was infused at a maximum rate of  $10 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  and NTP was infused to a maximum dose of less than 1 mg/kg in all NTP dogs except Group 4. In this later group, the mean dose of NTP administered was  $1.9 \pm 0.3$  (SEM) mg/kg (ranged from 1.2 to 3.4 mg/kg).

The rate of decrease in the CPP was controlled at approximately 5 mmHg/min by changing the rate of infusion of hypotensive drugs. When necessary, blood removal was used to achieve the desired CPP. The volume of blood removal was  $3.8 \pm 1.3$  (SEM) ml/kg in Group 1,  $2.9 \pm 2.0$  ml/kg in Group 2 of TMP dogs,  $1.9 \pm 1.1$  ml/kg in Group 1,  $5.5 \pm 1.0$  ml/kg in Group 2,  $3.3 \pm 1.4$  ml/kg in Group 3,  $2.5 \pm 1.6$  ml/kg in Group 4 of NTP dogs. There were no significant differences between corresponding groups and between Group 1 and 4 of NTP dogs. Positive end-expiratory pressure of 4 mmHg also was used to facilitate hypotension. For the restoration of CPP, the drugs were discontinued and blood was reinfused. If CPP did not return to approximately 90% of control by 20 min, phenylephrine (0.5 to 2.5 mg total) was administered to maintain CPP at near the control value. During the study, hemoglobin and rectal temperature were  $12.8 \pm 0.6$  (SEM) g/dl and  $37.4 \pm 0.3$  (SEM) °C, respectively. At each stage of hypotension, measurements of blood gas values, hemoglobin, and temperature were made at 5, 15, and 40 min, and of glycolytic metabolites at 15 min after the desired CPP

levels had been obtained. Posthypotension measurements were made at 25, 35, and 60 min, and of glycolytic metabolites at 35 min after the end of the hypotensive period. In Group 2 animals (both TMP and NTP), CSFP and glycolytic metabolites were not measured. The values of pressures and  $\text{PaO}_2$  shown in the tables are the mean of three determinations. Bicarbonate was administered intravenously during and after hypotension to maintain pH at near the control levels to a maximum dose of 3 mmol/kg.

Five minutes before the end of hypotension, EB 100 mg/kg (10%) was infused intravenously. After the last measurement in all groups except the Group 2 animals (both TMP and NTP), blood was drained from the jugular veins and the brain was perfused through both common carotid arteries at a perfusion pressure above 50 mmHg with normal saline while the heart was beating. The perfusion continued until the fluid efflux from both jugular veins became colorless. This was followed by a 10% formalin infusion for at least half an hour to fix the brain. If the heart beat did not cease during this maneuver, KCl was injected. In the Group 2 animals (both TMP and NTP), neurologic function was assessed by blind observers for three days by the score modified for dogs by Todd *et al.*<sup>8</sup> On the third day the brain was perfused first with saline and then with formalin, as in the other groups under halothane anesthesia (0.9% inspired). In all dogs, the brain was removed and stored in 10% formalin for a week. Cumulative distributions, extents, and areas of EB penetration on the dorsal cortical surface of the brain were recorded by blind observers. Standardized, serial coronal sections of 10-mm thickness were cut, and EB penetration score was calculated by drawing each section on a network ( $0.5 \text{ cm}^2$ ). The intensity of EB staining then was graded 1, 2, 3. EB penetration of each brain was calculated as a cumulative score.<sup>9</sup>

Statistical significance was tested by analysis of variance with critical difference testing, except for the comparison of EB penetration score, which was tested by Wilcoxon's rank-sum.<sup>10</sup>  $P < 0.05$  was considered significant.

## Results

The experimental conditions are shown in table 1 for TMP—Groups 1 and 2, in table 2 for NTP—Groups 1 and 2 and in table 3 for NTP—Groups 3 and 4. Cumulative distributions, extents, and areas of EB penetration on the dorsal cortical surface of the brain are shown in figure 1. Within each group, EB penetration was pronounced at around the lateral sagittal fissure. The neuroanatomic distributions and extents of EB penetration in cumulative coronal sections of brains in TMP—Group 1 and NTP—Group 1 are shown in figure 2, and the mean EB penetration score for all groups is shown in table 4 as a

TABLE 1. Experimental Conditions before, during, and after Hypotension with Trimethaphan

Group (n)	Parameters Measured	Before	Hypotension		After
1 (7)	Mean arterial pressure (mmHg)	104 ± 5	50 ± 2*	36 ± 1*	101 ± 4
	Cerebral perfusion pressure (mmHg)	99 ± 5	45 ± 2*	31 ± 1*	98 ± 4
	Cerebrospinal fluid pressure (mmHg)	5.5 ± 0.7	5.7 ± 0.5	5.5 ± 1.0	3.8 ± 0.8
	PaO <sub>2</sub> (mmHg)	202 ± 3	190 ± 4*	187 ± 4*	195 ± 2
	Arterial glucose (mg/dl)	114 ± 7	136 ± 14	167 ± 27*	122 ± 9
	Arterial lactate (mmol/l)	2.3 ± 0.3	3.1 ± 0.5	3.8 ± 0.6*	3.9 ± 0.7
	L/P	12.5 ± 1.3	16.7 ± 2.1	19.8 ± 3.0*	17.7 ± 1.8
2 (3)	Mean arterial pressure (mmHg)	119 ± 7	50 ± 2*	38 ± 2*	114 ± 11
	PaO <sub>2</sub> (mmHg)	242 ± 13	181 ± 7*	202 ± 31	240 ± 23

Values represent means ± standard errors of means.  
L/P: Lactate-pyruvate ratio.

\* Significantly different from before hypotension ( $P < 0.05$ ).

cumulative score in four coronal sections, the EB penetration was more pronounced in NTP-Group 1 than TMP-Group 1. The mean EB penetration score in NTP dogs given more than 1 mg/kg NTP did not differ significantly from that in dogs given less than 1 mg/kg. However, the EB penetration in NTP-Group 3 was significantly less than that in NTP-Group 1. Significant increases in CSFP were observed in all NTP groups but not with TMP. The time courses of CPP and CSFP after the end of the hypotensive period in both Group 1 dogs are shown in table 5. After the end of hypotension, CPP returned to control within 25 min and increased CSFP with NTP returned to control within 20 min. During hypotension with either drug, EEG remained active with variable changes in frequency and amplitude. With both drugs, arterial glucose, lactate, and lactate-pyruvate ratio (L/P) increased during and/or after hypotension except Group 3.

All animals in Group 2 given either TMP or NTP exhibited behavioral abnormalities, *i.e.*, extensor posturing, inability of placing, and impaired reaction to feeding for 6–24 h, but thereafter were neurologically normal.

### Discussion

The dye EB rapidly becomes bound to plasma albumin after intravenous injection and, as a result, does not pen-

etrate the normal BBB. In this study, in Groups 1, 3, and 4, EB was seen to have crossed the BBB and to have entered brain tissue either during the last 5 min of hypotension or during the recovery period of 60 min. The EB penetration was greater following NTP hypotension than TMP, suggesting that the former was associated with greater derangement of BBB function.

Our explanation for such impairment would be ischemia<sup>6</sup> occurring during the hypotensive period. The distribution of the dye staining in the boundary zones might be considered to suggest an ischemic basis for the BBB damage. However, there is much evidence that cerebral perfusion is better maintained during NTP than during TMP hypotension, and yet the dye staining was greater in the NTP experiments. Also, against this explanation is the limited damage that ischemia produces to the BBB in other experimental situations.<sup>11</sup> The possibility of ischemia-induced changes cannot be discarded completely, however, since most of the evidence concerning cerebral perfusion during NTP hypotension has been obtained by measuring cerebral blood flow in relatively large areas of brain. It is possible that local ischemia could occur in boundary zones, despite well-maintained overall perfusion if NTP were to produce steal of blood due to extreme vasodilation of the cerebral circulation.

An alternative and, in our view, more likely explanation

TABLE 2. Experimental Conditions before, during, and after Hypotension with Nitroprusside

Group (n)	Parameters Measured	Before	Hypotension		After
1 (7)	Mean arterial pressure (mmHg)	102 ± 3	58 ± 2*	45 ± 2*	110 ± 7
	Cerebral perfusion pressure (mmHg)	94 ± 3	45 ± 1*	32 ± 1*	103 ± 6
	Cerebrospinal fluid pressure (mmHg)	6.9 ± 1.1	12.1 ± 1.8*	12.9 ± 2.2*	7.6 ± 1.4
	PaO <sub>2</sub> (mmHg)	210 ± 5	203 ± 5	202 ± 4*	194 ± 1*
	Arterial glucose (mg/dl)	103 ± 9	129 ± 22	160 ± 30*	157 ± 29*
	Arterial lactate (mmol/l)	1.7 ± 0.1	2.2 ± 0.2	2.6 ± 0.3	3.6 ± 0.4*
	L/P	10.8 ± 0.8	16.1 ± 1.1	19.2 ± 1.3*	29.4 ± 4.4*
2 (3)	Mean arterial pressure (mmHg)	120 ± 0	60 ± 5*	47 ± 3*	119 ± 1
	PaO <sub>2</sub> (mmHg)	212 ± 10	205 ± 11	216 ± 21	210 ± 12

Values represent means ± standard errors of means.  
L/P: Lactate-pyruvate ratio.

\* Significantly different from before hypotension ( $P < 0.05$ ).

TABLE 3. Experimental Conditions before, during, and after Hypotension with Nitroprusside

Group (n)	Parameters Measured	Before	Hypotension		After
3 (7)	Mean arterial pressure (mmHg)	104 ± 7	58 ± 2*		110 ± 5
	Cerebrospinal perfusion pressure (mmHg)	97 ± 7	45 ± 1*		105 ± 7
	Cerebrospinal fluid pressure (mmHg)	6.7 ± 1.0	12.3 ± 1.1*		5.0 ± 1.4
	PaO <sub>2</sub> (mmHg)	199 ± 10	199 ± 9		208 ± 9
	Arterial glucose (mg/dl)	88 ± 5	124 ± 6		104 ± 8
	Arterial lactate (mmol/l)	1.1 ± 0.2	1.4 ± 0.3		1.7 ± 0.4
	L/P	15.2 ± 1.7	19.7 ± 3.9		25.3 ± 4.9
4 (7)	Mean arterial pressure (mmHg)	95 ± 6	53 ± 1*	42 ± 2*	98 ± 5
	Cerebral perfusion pressure (mmHg)	87 ± 6	43 ± 1*	31 ± 1*	89 ± 6
	Cerebrospinal fluid pressure (mmHg)	7.5 ± 0.4	10.3 ± 0.4*	10.5 ± 1.2*	8.6 ± 1.4
	PaO <sub>2</sub> (mmHg)	203 ± 3	202 ± 3	202 ± 3	195 ± 3*
	Arterial glucose (mg/dl)	122 ± 11	127 ± 11	186 ± 9*	137 ± 15
	Arterial lactate (mmol/l)	2.7 ± 0.2	3.3 ± 0.3	4.4 ± 0.6	5.2 ± 1.0*
	L/P	16.5 ± 1.7	20.0 ± 2.2	26.6 ± 3.8	28.3 ± 3.7*

Values represent means ± standard errors of means.  
L/P: Lactate-pyruvate ratio.

\* Significantly different from before hypotension ( $P < 0.05$ ).

for the EB penetration is that NTP-induced vasodilation opened up the capillary tight junctions. Relevant to this is the observation of Häggendal and Johansson<sup>12</sup> that BBB leakage of EB can be produced by the combination of papaverine and hypertension and that of Forster *et al.*<sup>9</sup> that EB leakage occurred when hypertension was induced rapidly during halothane administration. In the period immediately following the cessation of NTP infusion, autoregulation is impaired,<sup>13</sup> and therefore the capillaries are subjected to greater than normal intraluminal pres-

sure. Capillary tight junctions still might be open at this stage as a consequence of extreme vasodilation produced by NTP during profound hypotension. This explanation would account for the more extensive dye staining in the NTP, as compared with TMP experiments. However, it is hard to explain why considerable dye staining occurred in the boundary zones if this is the mechanism, though a similar pattern was observed by Forster *et al.*<sup>9</sup> in their study of norepinephrine-induced EB leakage during halothane anesthesia. The rate and extent of increase of

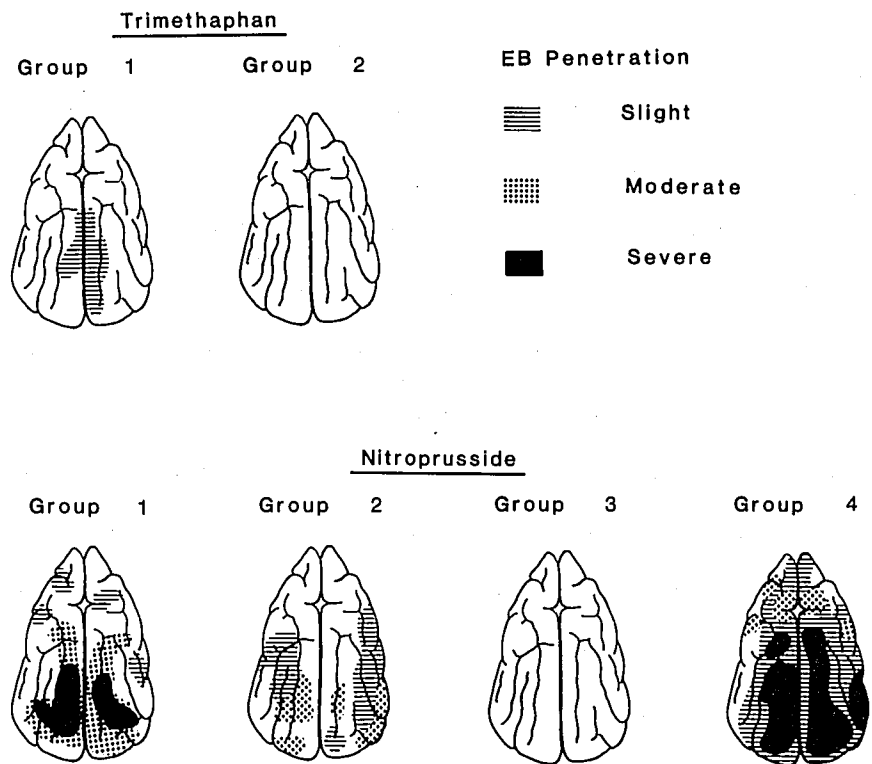


FIG. 1. Cumulative distributions, extents, and areas of EB penetration on the dorsal cortical surface of the brain in dogs subjected to induced hypotension with TMP or NTP. EB staining was pronounced at the lateral sagittal fissure in NTP dogs (*lower*).

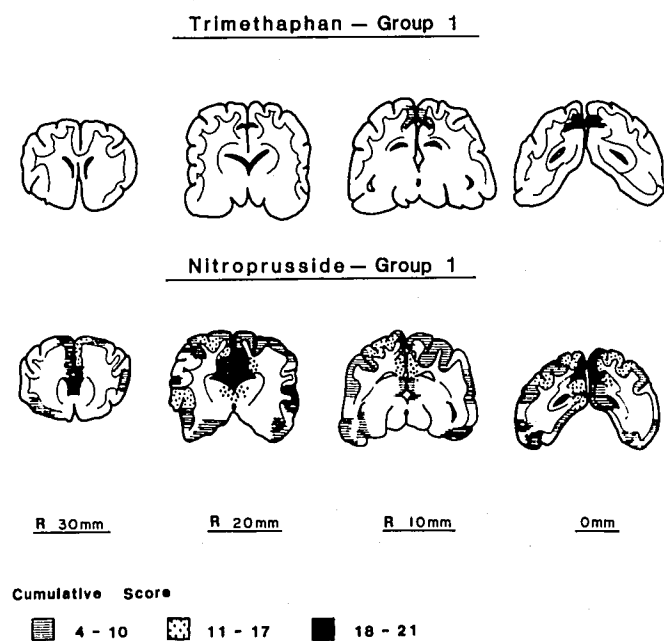


FIG. 2. The neuroanatomic distributions and extents of EB penetration in cumulative serial coronal sections (at 10-mm intervals rostral (R) to the interaural zero plane) of brains in TMP-Group 1 and NTP-Group 1. Cumulative scores in areas of 0.5 cm<sup>2</sup> were graded as shown in the key at the bottom.

CPP after cessation of NTP is important, since the quoted studies<sup>9,12</sup> of BBB function during halothane anesthesia, and with papaverine, have employed major and rapid increases in blood pressure to reveal EB leakage. For example, Forster *et al.*<sup>9</sup> increased blood pressure 40–155 mmHg in 5–40 s to demonstrate EB leakage during halothane anesthesia. In the present study, CPP returned to values no higher than control in the NTP-Group 1 animals over 20 min. This increase in CPP was about 5 min ahead of CPP recovery after TMP hypotension (table 5). The EB leakage therefore occurred after NTP hypotension, despite gradual recovery of CPP to normotensive values over 20 min. The extent of the increase

TABLE 4. Evans Blue Penetration Scores during Induced Hypotension

Group	n	Penetration Score
TMP-1	7	12 ± 6
NTP-1	7	105 ± 14*
TMP-2	3	0 ± 0
NTP-2	3	30 ± 7*†
NTP-3	7	6 ± 6†
NTP-4	7	125 ± 26

Values represent means ± standard errors of means. Statistical significance was tested by Wilcoxon's rank-sum. \* Between drugs ( $P < 0.05$ ). † From Group 1 ( $P < 0.05$ ).

in CPP after the end of hypotension would be considerable in the boundary zones, since pressure in these areas is known to be very low during hypotension. The prediction for EB extravasation in the boundary zones therefore might be due to a greater CPP increase in these sites during recovery.

It is necessary to be cautious in ascribing the changes observed only to opening of tight junctions in the BBB, since it is known that the control of large molecule transport is also dependent on pinocytosis in both directions across the endothelial cells. It is therefore possible that NTP might accelerate pinocytotic movement into the brain as has been suggested for several other drugs.<sup>14</sup>

In some situations in which EB crossed the BBB, plasma fluid crosses with it, due to the osmotic effect of the leaking plasma protein, this being one mechanism in the formation of vasogenic edema.<sup>15</sup> Direct measurements of brain water were not made in this study, but the volume of any associated vasogenic edema that may have occurred was not sufficient to elevate intracranial pressure above control values in the recovery period.

One technical factor is that, unless injected EB is completely bound to plasma albumin, some of it will cross the intact normal BBB. We should suggest that the absence of extravasation of EB in the TMP-Group 2 dogs studied 3 days after hypotension demonstrates that, in this study with the doses of EB used, failure of binding to plasma albumin did not occur to any significant extent. Furthermore, the lack of penetration of EB in the group studied three days after NTP hypotension (Group 2) indicates that the BBB damage seen early after hypotension resolves within this period of time.

As usual in animal experimentation, the interpretation of the findings should include consideration of the type of anesthesia used, in this case halothane. Forster *et al.*,<sup>9</sup> using methods for quantification of BBB leakage that we have followed largely, showed that rapid norepinephrine-induced hypertension produced greater EB leakage during halothane as compared with thiopental anesthesia. They postulated, as we have done in this article, that the leakage was due to cerebral vasodilation. The halothane anesthesia employed in the present experiments may have been responsible for part of the EB leakage, though the animals were not subjected to hypertension in the recovery period of the extent or rapidity of that used by Forster *et al.*<sup>9</sup> Halothane, however, could not account for the difference observed in EB leakage between NTP and TMP hypotension.

Factors that must be considered other than background anesthesia are the volume of blood removal and the application of PEEP. The volume of blood removal was similar in all experimental groups and was small when considered in comparison with normal intraoperative blood losses. The application of PEEP must have elevated

TABLE 5. Time Courses of Cerebral Perfusion Pressure (CPP) and Cerebrospinal Fluid Pressure (CSFP) after Injection of Evans Blue in Group 1

Drug	Pressure (mmHg)	Before	Time after End of Hypotension (min)					
			-5	0	5	15	20	25
TMP	CPP	99 ± 5	32 ± 1*	32 ± 3*	39 ± 4*	57 ± 6*	72 ± 7*	98 ± 5
	CSFP	5 ± 1	5 ± 1	4 ± 1	3 ± 1	3 ± 1	5 ± 1	4 ± 1
NTP	CPP	94 ± 3	32 ± 1*	32 ± 1*	46 ± 5*	77 ± 6*	91 ± 10	104 ± 6
	CSFP	7 ± 1	13 ± 2*	13 ± 2*	13 ± 2*	10 ± 2	9 ± 1	8 ± 2

Values represent means ± standard errors of means.  
-5: Evans blue injection.

0: End of hypotensive period.  
\* Significantly different from control ( $P < 0.05$ ).

cerebral venous pressure but only to a small degree, since the value of PEEP was 4 mmHg and since the animals were placed with the head above thorax level. In respect of these factors, it is not possible to exclude some interaction with drug-induced hypotension, but any influence must have been exerted on each experimental group and so could not account for the differences observed between NTP and TMP.

In summary, NTP causes more pronounced dysfunction of BBB than TMP at comparable levels of hypotension.

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