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Canine Systemic and Cerebral Effects of Hypotension Induced by Hemorrhage, Trimethaphan, Halothane, or Nitroprusside

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In 62 dogs, hypotension to a mean arterial pressure of either 40 or 50 torr (equivalent to a cerebral perfusion pressure of 30 or 40 torr, respectively) for one hour was induced by hemorrhage (oligemia), trimethaphan, halothane, or sodium nitroprusside. Before and during the period of hypotension, the following were measured: mean arterial blood pressure, cardiac output, whole-body O_2 consumption, cerebral blood flow, cerebral O_2 consumption, arterial blood gases, blood O_2 content, and lactate, pyruvate, glucose, epinephrine, and norepinephrine concentrations. At the end of the period of hypotension, brain biopsies were taken for determination of adenosine triphosphate, phosphocreatine, lactate, and pyruvate concentrations. In an additional eight dogs following one hour of hypotension (at 40 torr) induced by one of the four techniques, the brains were perfused with carbon black, removed, and examined. In another ten dogs following hypotension (at 40 torr) induced with either halothane or trimethaphan, the animals were observed for three days and then killed for examination of the brain.

Dogs maintained at a mean arterial pressure of 40 torr, despite differences in cerebral blood flow, demonstrated metabolic disturbances compatible with systemic and cerebral hypoxia. These were greatest in those dogs given nitroprusside in excess of 1.0 mg/kg, presumably due to cyanide toxicity. In dogs maintained at 50 torr, metabolic disturbances were minimal or absent in the halothane- and nitroprusside-treated dogs but were still apparent in the oligemic and trimethaphan-treated dogs. Carbon black infusions revealed no evidence of nonhomogeneous flow. Three of the ten dogs observed for three days had persistent post-hypotension neurologic dysfunction. Two of these were given trimethaphan. The results suggest that the systemic and cerebral effects of halothane and nitroprusside (at doses <1.0 mg/kg) are similar and at a mean arterial pressure of 50 torr are of little consequence. By contrast, hypotension induced by trimethaphan or oligemia results in detectable metabolic alterations even at a pressure of 50 torr.
(Key words: Anesthetic techniques, hypotensive; Brain, blood flow; Brain, metabolism; Sympathetic nervous system, ganglionic blocking agents, trimethaphan; Pharmacology, nitroprusside; Anesthetics, volatile, halothane; Shock, cerebral blood flow; Hemorrhage, cerebral blood flow.)

A WIDE VARIETY of clinical techniques has been used to induce arterial hypotension to facilitate surgical procedures and lessen blood loss. All approaches are based ultimately upon various degrees and combinations of reductions in circulating blood volume, cardiac output, and peripheral vascular resistance. The original technique of oligemic hypotension has been replaced today by the use of ganglionic blockers (usually trimethaphan), deep general anesthesia (usually halothane), or, most recently, direct vasodilation with sodium nitroprusside. Each of these techniques has advantages and disadvantages which, on balance, do not permit identification of a "preferred" technique. Theoretically, the ideal technique would result in the most controllable, lowest arterial pressure with the least possibility of cerebral or other organ hypoxic damage. Most investigators concerned with induced hypotension have examined hemodynamic effects, and based upon comparative flow measurements (usually cardiac output or individual organ blood flow—most importantly, cerebral blood flow), have suggested preference for one technique over another. Sodium nitroprusside has recently received considerable attention, in part because of several studies that have demonstrated little or no reduction in cardiac output[1–3] and/or cerebral blood flow (CBF)[4,5] during

ABBREVIATIONS

CBF	= cerebral blood flow
$C(a - ss)_{O_2}$	= arterial–sagittal sinus blood O_2 content difference
CMR_{O_2}	= cerebral metabolic rate for oxygen
$\dot{Q}$	= cardiac output
$C(a - \bar{v})_{O_2}$	= arterial–mixed venous blood O_2 content difference
$\dot{V}_{O_2}$	= whole-body O_2 consumption
MAP	= mean arterial blood pressure
ATP	= adenosine triphosphate
PCr	= phosphocreatine
L/P	= lactate–pyruvate ratio

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nitroprusside hypotension. Enthusiasm for this drug has in part been countered by growing recognition of potential toxicity because of cyanide release.[6–8] Additionally, the assumption that because blood flow is relatively high (at a given reduced blood pressure), tissue hypoxia is correspondingly less need not be correct. Maldistribution of flow is one example of a circumstance in which an elevated or maintained total flow does not mean flow is adequate.

In recent canine studies, Yashon *et al.*[9] compared trimethaphan, halothane, and oligemic hypotension and concluded that halothane was the superior technique, based primarily upon differences in cerebral tissue lactate concentrations. In another report, they[10] suggested a possible cerebral toxic effect of trimethaphan distinct from the effects of the hypotension *per se*. No report comparing both the systemic and cerebral hemodynamic and metabolic effects of the different basic hypotensive techniques is available. The present study was designed to provide comparisons at two levels of hypotension induced by hemorrhage, trimethaphan, halothane, or nitroprusside.

Methods

Sixty-two unmedicated mongrel dogs weighing 12–20 kg were studied. Anesthesia was induced and initially maintained with halothane (1.0 per cent inspired) in nitrous oxide (70 per cent) and oxygen. Muscle paralysis for endotracheal intubation was produced with succinylcholine, 20 mg, and then maintained with an infusion of 150 mg/hr. Catheters were inserted into both femoral veins for drug, blood, and fluid infusions, into both femoral arteries for pressure measurements and blood sampling, and into the pulmonary artery for dye injections and blood sampling. A thermistor was inserted in the right atrium for body temperature measurement. Thereafter, the animal was placed in the prone position with the head elevated and supported on a block 15 cm in height (equivalent to a pressure differential between heart and brain of approximately 10 torr). The sagittal sinus was exposed, isolated from extracerebral communications, and cannulated as previously described[11] for direct measurement of cerebral blood flow (CBF) and cerebral arterial–sagittal sinus blood oxygen content differences [$C(a\text{-}ss)_{O_2}$]. The reservoir for collection of sagittal-sinus blood was maintained level with the sinus, resulting in a draining venous pressure of zero. A parietal epidural thermistor was inserted for measurement of brain temperature. Following completion of the surgical preparation, inspired halothane was adjusted to result in an expired halothane concentration of 0.1 per cent (Beckman infrared analyzer); N_2O (approximately 70 per cent) was continued; ventilation and inspired oxygen were adjusted to result in a Pa_{CO_2} of 40 ± 1 torr (mean ± SE) and a Pa_{O_2} of 150 ± 4 torr; buffer base was adjusted to 50 ± 1 mEq/l by administration of sodium bicarbonate; body and brain temperatures were adjusted to 37.0 ± 0.1 C by heat lamps.

When the above control conditions were stable (after 30–45 minutes), control measurements were made over a 30-minute period. CBF and $C(a\text{-}ss)_{O_2}$ were measured at 5-minute intervals. Cardiac output ($\dot{Q}$) and arterial–mixed venous blood O_2 content differences [$C(a\text{-}\bar{v})_{O_2}$] were measured in duplicate at 15-minute intervals and arterial blood samples were taken for determination of lactate, pyruvate, glucose, epinephrine, and norepinephrine concentrations. Cerebral metabolic rate for O_2 (CMR_{O_2}) and whole-body O_2 consumption ($\dot{V}_{O_2}$) were calculated as products of the respective flow and $C(a\text{-}\dot{v})_{O_2}$ measurements. Blood O_2 contents were calculated from blood P_{O_2} and oxyhemoglobin concentrations (IL CO-oximeter). Cardiac output was calculated from dye-dilution curves obtained by injecting indocyanine green into the pulmonary artery and subsequent continuous sampling from a femoral artery through a calibrated densitometer (Waters-400). Blood glucose, lactate, and pyruvate concentrations were determined by an enzymatic method. Plasma epinephrine and norepinephrine concentrations were determined by the trihydroxyindole method.[12] Arterial blood pressure was transduced by a strain gauge with the zero reference level at the level of the heart.

Following control determinations, dogs were divided into two major groups, each containing four subgroups. In 36 dogs, the mean arterial pressure (MAP) was reduced (over a 2–5-minute period) to 40 torr using one of four techniques: hemorrhage (10 dogs), trimethaphan infusion (9 dogs), deep halothane anesthesia (9 dogs), or sodium nitroprusside infusion (8 dogs). In 26 dogs, MAP was reduced to 50 torr using the same four techniques: hemorrhage (5 dogs), trimethaphan (9 dogs), halothane (6 dogs), or nitroprusside (6 dogs). These pressure levels were equivalent to cerebral perfusion pressures of approximately 30 and 40 torr, respectively (because of the 15-cm elevation of the brain). In every dog, the selected pressure of 40 or 50 torr was maintained for one hour. With hemorrhage, an arterial line was opened to a pressurized reservoir set at the level of pressure desired, and the blood loss was 400–800 ml. With trimethaphan, a 0.2 per cent solution was infused until the desired pressure was achieved (the total dose was 30–200 mg), and in a few dogs, the development of tachyphylaxis necessitated the addition of an expiratory resistance of 3–10 cm H_2O to maintain the desired MAP. With deep halothane anesthesia, the inspired concentrations ranged from 1.0 to 3.5 per cent. With sodium nitroprusside, a 0.02 per

TABLE 1. Initial and Final Values for *p*H, Buffer Base, and Hemoglobin at MAP of 40 or 50 Torr as Produced by Oligemia, Trimethaphan, Halothane, or Nitroprusside (Mean ± SE)

	Oligemia		Trimethaphan		Halothane		Nitroprusside	
	Initial	Final	Initial	Final	Initial	Final	Initial	Final
MAP ≈ 40 torr	(n = 10)		(n = 9)		(n = 9)		(n = 8)	
*p*H	7.41 ± 0.01	7.12‡ ± 0.05	7.41 ± 0.01	7.26 ± 0.02	7.40 ± 0.01	7.28 ± 0.02	7.39 ± 0.01	7.25 ± 0.03
BB^+, mEq/l	50 ± 1	33‡ ± 2	50 ± 1	41 ± 1	49 ± 0	42 ± 1	49 ± 0	39 ± 2
Hb, g/dl	15.9 ± 0.7	13.1 ± 0.5	15.9 ± 0.8	13.9 ± 0.8	16.8 ± 0.7	14.7 ± 0.5	15.0 ± 0.8	12.6 ± 0.8
MAP ≈ 50 torr	(n = 5)		(n = 9)		(n = 6)		(n = 6)	
*p*H	7.44 ± 0.01	7.31* ± 0.03	7.43 ± 0.01	7.34* ± 0.02	7.42 ± 0.02	7.39†* ± 0.03	7.41 ± 0.01	7.29 ± 0.02
BB^+, mEq/l	50 ± 1	43* ± 1	50 ± 1	45* ± 1	50 ± 1	48†* ± 1	49 ± 1	43 ± 1
Hb, g/dl	16.7 ± 0.7	14.3 ± 0.7	17.9 ± 0.5	16.7 ± 0.8	17.1 ± 0.5	14.5 ± 0.4	17.0 ± 0.6	15.3 ± 0.6

* Significantly higher than final values at MAP ≈ 40 torr, $P < 0.05$.
† Final values *not* significantly different from initial values; all other final values are significantly less than initial values, $P < 0.05$.
‡ Significantly less than all other final values, $P < 0.05$.

cent solution was infused as needed to maximum doses of 2.5 mg/kg for MAP 40 torr and 1.0 mg/kg for MAP 50 torr. Approximately half of these animals proved to be resistant to the nitroprusside, and in these an expiratory resistance of 5–10 cm H_2O was added. In two animals from each group, the desired hypotensive level could not be achieved, and as much as 200 ml of blood was removed to maintain the desired MAP.

During the one-hour period of hypotension, CBF and $C(a\text{-}ss)O_2$ were measured at 5-minute intervals, $\dot{Q}$ and $C(a\text{-}\bar{v})_{O_2}$ were measured at 15-minute intervals, and samples for blood lactate, pyruvate, and glucose were taken at 15-minute intervals. At the end of an hour, final measurements were made and blood samples taken, including a sample for plasma epinephrine and norepinephrine determinations. Thereafter, the dura was exposed and incised and simultaneous bilateral biopsies were taken from the cerebral hemispheres using a technique that deposits a 200–400-mg core of tissue into liquid nitrogen within one second.[13] Brain samples were subsequently analyzed for concentrations of adenosine triphosphate (ATP, firefly bioluminescent technique),[14] phosphocreatine (PCr, fluorometric technique),[15] and lactate and pyruvate (enzymatic techniques).

In studies of eight additional dogs, the anesthetic management, control conditions, and schedule were identical to those described above, but no surgical procedure was done other than cannulation of a femoral artery and vein. MAP was reduced and maintained at 40 torr for an hour in two dogs by each of the four techniques. After an hour, the chest was opened, the ascending aorta and superior vena cava were cannulated, and the descending aorta was ligated. The vasculature supplied by the ascending aorta was then flushed with saline solution (approximately 1,000 ml) at a pressure of 40 torr until superior vena-caval drainage was clear, following which 500 ml of filtered carbon black and 500 ml of 10 per cent formalin were simultaneously infused into the ascending aorta at a pressure of 40 torr. Two hours later the brains were removed and stored in formalin for subsequent examination.

In ten additional dogs, hypotension of 40 torr for an hour was induced with either halothane or trimethaphan (5 dogs each). Following this, each animal was allowed to recover from anesthesia, observed for three days, and then killed. The brain was removed, fixed in formalin, and examined for gross abnormalities.

Results were analyzed statistically using Student's t test for paired data to compare initial (control) and final values in the same dog and Student's t test for unpaired data for comparing final values in animals made hypotensive by the same technique to a MAP of either 40 or 50 torr. Significant differences in final values among the different hypotensive techniques in either the 40-torr or 50-torr groups were determined by analysis of variance and critical-difference testing. For all, a probability of less than 5 per cent that differences were due to chance was considered significant.

Results

Although numerous measurements and calculations were made in each group of dogs, pertinent results can be most readily grasped by examining the initial (control) and final values in each group and by comparing final values in the various groups. Significant metabolic acidosis developed in all groups except those in which MAP was reduced to 50 torr with halothane (table 1). The most severe acidosis developed with a reduction to 40 torr by hemorrhage. With the exception of the nitroprusside group, acidosis was significantly less in animals in which MAP was reduced to 50 torr compared with those in which MAP was reduced to 40 torr. In all eight groups of animals, there were significant reductions in hemoglobin following an hour of hypotension, which presumably reflects both the

large number of blood samples and a compensatory hemodilution during hypotension.

With reduction in MAP, whether to 40 or 50 torr, there was a significant reduction in $\dot{Q}$, which exceeded 50 per cent in all groups (tables 2 and 3). The lowest cardiac outputs were observed in the oligemic animals (80 and 75 per cent decreases, respectively), but the mean reductions with halothane in the 40-torr animals and with trimethaphan and nitroprusside in the 50-torr animals approached

TABLE 2. Systemic Hemodynamic and Metabolic Values at MAP ≈ 40 Torr (Mean ± SE)

	Oligemia		Trimethaphan		Halothane		Nitroprusside	
	Initial	Final	Initial	Final	Initial	Final	Initial	Final
MAP, torr	124 ± 4	41 ± 1	127 ± 4	41 ± 1	120 ± 5	43 ± 2	125 ± 5	43 ± 3
$\dot{Q}$, l/min/m²	3.29 ± 0.22	0.68 ± 0.12	3.82 ± 0.19	1.57 ± 0.15	2.84 ± 0.25	0.97 ± 0.13	3.03 ± 0.20	1.46 ± 0.23
$\dot{V}_{O_2}$, ml/min/m²	154 ± 6	82 ± 8	179 ± 7	130 ± 8	168 ± 3	103 ± 6	150 ± 6	105 ± 7
$P\bar{v}_{O_2}$, torr	56 ± 2	28‡ ± 1	57 ± 2	44 ± 3	50 ± 2	38 ± 2	54 ± 2	44 ± 5
Lactate, μm/ml	3.80 ± 0.43	10.78‡ ± 1.33	3.63 ± 0.43	3.73† ± 0.08	2.91 ± 0.16	4.28 ± 0.49	3.44 ± 0.27	6.55 ± 1.17
L/P	13 ± 1	46 ± 8	12 ± 1	13† ± 2	12 ± 1	24 ± 3	14 ± 1	36 ± 7
Glucose, mg/dl	118 ± 5	284 ± 36	114 ± 8	100† ± 14	118 ± 6	100† ± 10	135 ± 14	220 ± 41
Epinephrine, ng/ml	1.86 ± 0.45	24.17 ± 7.96	3.18 ± 0.62	2.42† ± 0.53	1.12 ± 0.27	0.34† ± 0.03	2.80 ± 0.33	4.95 ± 0.78
Norepinephrine, ng/ml	0.31 ± 0.19	4.62 ± 3.41	0.48 ± 0.02	1.33† ± 0.25	0.24 ± 0.02	0.29† ± 0.01	0.42 ± 0.09	2.57 ± 0.73
Total catecholamines, ng/ml	2.17 ± 0.64	28.79 ± 21.36	3.66 ± 0.64	3.75† ± 0.28	1.36 ± 0.28	0.63† ± 0.02	3.22 ± 0.33	7.53 ± 0.99

† Final values *not* significantly different from initial values; all other final values differ significantly ($P < 0.05$) from initial values.
‡ Significantly different from all other final values, $P < 0.05$.

TABLE 3. Systemic Hemodynamic and Metabolic Values at MAP ≈ 50 Torr (Mean ± SE)

	Oligemia		Trimethaphan		Halothane		Nitroprusside	
	Initial	Final	Initial	Final	Initial	Final	Initial	Final
MAP, torr	123 ± 7	51 ± 0	130 ± 5	51 ± 1	136 ± 6	50 ± 1	131 ± 3	50 ± 1
$\dot{Q}$, l/min/m²	3.18 ± 0.46	0.77 ± 0.04	3.39 ± 0.33	1.00 ± 0.05	3.26 ± 0.37	1.19 ± 0.11	2.94 ± 0.35	0.86 ± 0.11
$\dot{V}_{O_2}$, ml/min/m²	168 ± 6	104 ± 6	171 ± 7	109 ± 5	181 ± 10	106 ± 6	164 ± 11	107 ± 11
$P\bar{v}_{O_2}$, torr	59 ± 5	33 ± 3	57 ± 2	41 ± 2	55 ± 3	41 ± 3	55 ± 2	38 ± 1
Lactate, μm/ml	3.48 ± 0.27	5.41†* ± 0.97	4.85 ± 0.52	4.06† ± 0.40	3.55 ± 0.61	3.01† ± 0.34	3.78 ± 0.45	4.81 ± 0.55
L/P	13 ± 1	22†* ± 5	15 ± 1	16† ± 1	15 ± 1	16† ± 1	13 ± 1	20 ± 2
Glucose, mg/dl	123 ± 8	163† ± 23	146 ± 13	106† ± 9	148 ± 11	111† ± 8	125 ± 8	142† ± 18
Epinephrine, ng/ml	2.40 ± 0.36	6.12 ± 1.40	1.50 ± 0.37	1.45† ± 0.34	1.63 ± 0.41	2.25† ± 1.30	2.88 ± 1.13	5.48 ± 1.20
Norepinephrine, ng/ml	0.63 ± 0.13	1.31 ± 0.29	0.69 ± 0.13	0.99† ± 0.27	0.65 ± 0.21	0.76† ± 0.24	0.35 ± 0.03	1.42 ± 0.25
Total catecholamines, ng/ml	3.03 ± 0.25	7.43 ± 1.58	2.19 ± 0.37	2.44† ± 0.38	2.28 ± 0.42	3.01† ± 1.40	3.23 ± 1.11	6.90 ± 1.35

* Values significantly different from final values at MAP ≈ 40 torr, $P < 0.05$.
† Final values *not* significantly different from initial values; all other final values differ significantly ($P < 0.05$) from initial values.

TABLE 4. Cerebral Hemodynamic and Metabolic Values at MAP ≈ 40 Torr (Mean ± SE)

	Oligemia		Trimethaphan		Halothane		Nitroprusside	
	Initial	Final	Initial	Final	Initial	Final	Initial	Final
CBF, ml/100 g/min	105 ± 8	45§ ± 5	98 ± 8	32 ± 2	91 ± 7	31 ± 3	95 ± 7	50§ ± 6
Pss_{O_2}, torr	64 ± 2	38 ± 3	62 ± 1	27 ± 2	57 ± 2	39 ± 4	59 ± 3	42 ± 4
CMR_{O_2}, ml/100 g/min	4.88 ± 0.40	4.61† ± 0.38	5.26 ± 0.34	4.38 ± 0.17	4.86 ± 0.28	3.48‡ ± 0.27	4.69 ± 0.34	4.24† ± 0.43
Lactate, μm/g	(2.06* ± 0.20)	4.15 ± 0.83		5.00 ± 0.67		5.80 ± 0.58		6.77 ± 1.81
L/P	(15* ± 2)	27 ± 4		28 ± 6		33 ± 5		30 ± 7
ATP, μm/g	(2.24* ± 0.03)	1.94 ± 0.05		2.01 ± 0.09		1.78 ± 0.08		1.69 ± 0.07
PCr μm/g	(4.96* ± 0.41)	2.13 ± 0.18		2.51 ± 0.35		2.30 ± 0.22		1.80 ± 0.28

* Previously reported normal values.[14,21]

† Final values *not* significantly different from initial; all other final values differ significantly from initial values or from previously reported control values for brain lactate, L/P, ATP and PCr, $P < 0.05$.

‡ Significantly different from all other final values, $P < 0.05$.

§ Significantly higher than halothane and trimethephan values, $P < 0.05$.

similar values. The reductions in $\dot{Q}$ did not differ significantly between the 40-torr and 50-torr groups made hypotensive by the same technique. Reductions in $\dot{V}_{O_2}$ paralleled, but did not match, the reductions in $\dot{Q}$, and this was reflected by significant reductions in $P\bar{v}_{O_2}$ in all groups. The reductions in $\dot{Q}$ and $\dot{V}_{O_2}$ were concomitant with the reduction in MAP and tended to remain constant during the hour of hypotension. In the 40-torr groups, blood lactate and L/P were significantly elevated in all but the trimethaphan-treated animals. In the 50-torr groups, only the nitroprusside-treated animals developed significant elevations of blood lactate. Catecholamine levels (both epinephrine and norepinephrine) were significantly elevated in the oligemic animals and the nitroprusside-treated animals at both blood pressure levels. This was accompanied by elevated glucose concentrations in these four groups (not significant in the 50-torr animals).

CBF significantly decreased in all groups (tables 4 and 5). The largest reductions were observed in animals at 40 torr with halothane or trimethaphan (66 and 67 per cent, respectively). Only in the halothane-treated animals was there a significant improvement in CBF at 50 torr compared with 40 torr, although mean values were higher at 50 torr for all groups. The reduction in CBF was concomitant with the reduction in MAP and tended to remain constant during the hour of hypotension. CMR_{O_2} significantly decreased in the animals made hypotensive with halothane (at both 40 and 50 torr); this is presumably explained by a direct effect of halothane. In the remaining groups in which MAP was reduced to 40 torr, there was a tendency for CMR_{O_2} to decrease throughout the one-hour period of hypotension, and this was significant at the end of an hour in the trimethaphan-treated animals. In the animals maintained at 50 torr, there was no tendency for CMR_{O_2} to decrease.

Brain concentrations of ATP, PCr, lactate, and the L/P were significantly abnormal in all dogs in which MAP was reduced to 40 torr for an hour. The extents of alterations from normal were similar in all four groups. In animals maintained at 50 torr for an hour, differences between the groups were observed. Lactate was significantly elevated only in the trimethaphan-treated animals. ATP was also significantly reduced in the trimethaphan-treated animals, as well as the oligemic animals. In all animals, PCr was significantly below normal levels.

In the group of eight dogs kept hypotensive at 40 torr for an hour (two with each technique) and then perfused with carbon black, there was no apparent abnormality or difference among the animals. The distribution of carbon black was homogeneous throughout the cortical gray matter, including the watershed zones.

In three of the ten dogs kept hypotensive at 40 torr for an hour with either halothane or trimethaphan (five animals each) and then observed for three days, functional abnormalities were observed. One of the trimethaphan-treated animals remained unconscious and died on the second day; at necropsy the brain was grossly edematous. Another trimethaphan-treated animal was hemiparetic (−2), but no gross cerebral infarction was found. One halothane-treated dog remained disoriented for the three days, but again no infarction was found. The remaining dogs appeared lethargic for the first 24–48 hours but otherwise appeared grossly normal, as did the brains at necropsy.

Discussion

Examination of the hemodynamic effects ($\dot{Q}$ and CBF) of induced hypotension as produced by the various techniques used in this study might be somewhat misleading. The control anesthetic condition selected (70 per cent nitrous oxide, 0.1 per cent halothane) can be expected (at least in the dog) to result in a hyperdynamic state, such that control values for both $\dot{Q}$ and CBF are unusually high. The mean control $\dot{Q}$ (for all eight groups) was 3.2 l/min/m², compared with a normal value of about 2.6 l/min/m² in dogs lightly anesthetized with halothane (0.8 per cent expired).[16] Similarly, the mean control CBF was 99 ml/100 g/min, whereas the normal value in dogs equilibrated at 0.8 per cent halothane is about 70 ml/100 g/min.[17] Thus, the observed percentage reductions in both $\dot{Q}$ and CBF in this study with induction of hypotension should be viewed as exaggerated. Nonetheless, the reduction was real and would be significant whichever values one used as control values. Surprisingly, in terms of the systemic hemodynamic effects, there is little to choose between the four techniques or between hypotension at 40 or 50 torr. By contrast, CBF's at 40 torr were significantly higher with nitroprusside and oligemia, and at 50 torr mean CBF values were higher for all techniques than at 40 torr (significantly so with halothane). Contrary to previous reports,[1-3] there was no suggestion that $\dot{Q}$ was better preserved with nitroprusside. This may be explained in part by the need for blood removal and/or added expiratory resistance in about half of the animals given nitroprusside. Predictably, elevations of blood catecholamine levels were observed only in the oligemic and nitroprusside-treated dogs. In the halothane- and trimethaphan-treated dogs, this response was presumably blocked by the drugs themselves. The observation that (at the same low perfusion pressures) animals with elevated catecholamines had the highest CBF's may be more than coincidental. However, at normal or increased perfusion pressures there is no consistent evidence that catecholamines directly alter cerebrovascular resistance.

Examination of the metabolic effects is more revealing. At a mean arterial pressure of 40 torr, all animals developed significant metabolic acidosis. The cerebral effects at this pressure (equivalent to a perfusion pressure of 30 torr) were similar: reductions in both CMR_{O_2} and brain energy stores, with cerebral lactic acidosis. The magnitudes of deviations from normal were similar in all four groups and apparently were not influenced by the consistently higher CBF values in the oligemic and nitroprusside-treated dogs. The greater reduction in CMR_{O_2} in the halothane-treated dogs appeared to offer no protection in terms of the metabolic alterations produced. This is not in-

TABLE 5. Cerebral Hemodynamic and Metabolic Values at MAP ≈ 50 Torr (Mean ± SE)

	Oligemia		Trimethaphan		Halothane		Nitroprusside	
	Initial	Final	Initial	Final	Initial	Final	Initial	Final
CBF, ml/100 g/min	95 ± 9	56 ± 7	97 ± 7	40† ± 4	109 ± 10	52* ± 2	101 ± 9	55 ± 4
Pss_{O_2}, torr	63 ± 4	42 ± 3	61 ± 2	33† ± 2	61 ± 4	42 ± 3	61 ± 4	41 ± 2
CMR_{O_2}, ml/100 g/min	5.63 ± 0.45	5.79† ± 0.48	5.47 ± 0.44	5.44†* ± 0.36	5.04 ± 0.43	4.52†* ± 0.42	5.42 ± 0.29	5.95†* ± 0.27
Lactate, μm/g	(2.06 ± 0.20)	2.53† ± 0.47		3.50 ± 0.27		2.51†* ± 0.06		2.95† ± 0.34
L/P	(15 ± 2)	10† ± 2		12† ± 3		10†* ± 1		11† ± 4
ATP, μm/g	(2.24 ± 0.03)	1.88 ± 0.15		2.03 ± 0.08		2.25†* ± 0.07		2.20†* ± 0.07
PCr, μm/g	(4.96 ± 0.41)	2.11 ± 0.28		2.40 ± 0.21		3.00 ± 0.21		2.21 ± 0.15

* Values significantly different, $P < 0.05$, from final values at MAP ≈ 40 torr.
† Final values *not* significantly different from initial values or previously reported control values (for lactate, L/P, ATP, and PCr); all other final values differ significantly, $P < 0.05$, from initial values.
‡ Significantly different from all other final values, $P < 0.05$.

TABLE 6. Final Values in Dogs Given Nitroprusside in Total Doses of Either < or >1 mg/kg at MAP ≈ 40 Torr (Mean ± SE)

	<1.0 mg/kg (n = 4)	>1.0 mg/kg (n = 4)
Nitroprusside, mg/kg	0.6 ± 0.2	2.1* ± 0.5
*p*H	7.31 ± 0.03	7.18* ± 0.03
BB, mEq/l	42 ± 1	37* ± 2
$P\bar{v}_{O_2}$, torr	35 ± 4	54* ± 6
Q̇, l/min/m²	1.09 ± 0.25	1.83 ± 0.31
$\dot{V}_{O_2}$ ml/min/m²	100 ± 9	110 ± 11
Blood lactate, μm/ml	4.58 ± 0.89	8.53* ± 1.72
Blood L/P	24 ± 5	49* ± 9
Pss_{O_2}, torr	34 ± 3	50* ± 6
CBF, ml/100 g/min	51 ± 12	49 ± 6
CMR_{O_2}, ml/100 g/min	4.88 ± 0.70	3.60* ± 0.33
Brain lactate, μm/g	3.18 ± 0.47	10.35* ± 2.53
Brain L/P	16 ± 5	41* ± 10
ATP, μm/g	1.72 ± 0.06	1.67 ± 0.13
PCr, μm/g	2.34 ± 0.30	1.25 ± 0.26

* Significantly different from <1.0 mg/kg values ($P < 0.05$).

consistent with the reported effects of halothane in regional cerebral ischemia, wherein the pathologic and metabolic effects appear to be aggravated in the presence of halothane rather than alleviated.[18,19]

An overall examination of the cerebral effects at the end of an hour of hypotension at MAP 40 torr suggests that of the four techniques used, nitroprusside had the most deleterious effects. Despite the highest mean value for CBF (50 ml/100 g/min), the mean values for ATP and PCr were the lowest and that for brain lactate, the highest (however, differences were not significant). In this group, we had preset a maximum of a total dose of 2.5 mg/kg of nitroprusside, based upon the observation by McDowall *et al.*[6] indicating that a total dose somewhere between 1.6 and 4.9 mg/kg was toxic in the baboon. As in the baboon, we found that half of the dogs studied (four of eight) were relatively sensitive to nitroprusside (requiring total doses of only 0.25–0.8 mg/kg), whereas the remainder were relatively resistant, requiring larger doses along with added expiratory resistance and, in two of the four, blood removal. In this large-dose group, two of the animals received the maximum dose (2.5 mg/kg) and in the other two, doses of 1.2 and 2.0 mg/kg, respectively, were given. Dividing the animals into two groups according to dose given (that is, doses less than and doses greater than 1.0 mg/kg) reveals significant differences in the systemic and cerebral metabolic effects (table 6). In the high-dose animals, metabolic acidosis was more severe, CMR_{O_2} was significantly reduced, cerebral lactic acidosis was three times that in the low-dose animals, and both $P\bar{v}_{O_2}$ and Pss_{O_2} were significantly higher. The results suggest a direct toxic effect of nitroprusside over and above the effects of hypotension at doses exceeding 1.0 mg/kg. The alterations observed are compatible with cyanide toxicity in that despite evidence of tissue hypoxia, draining venous blood was well oxygenated. This is compatible with an interference with tissue O_2 uptake such as occurs with inactivation of cytochrome oxidase by cyanide. Thus, it appears that in the dog (unlike the baboon), cyanide toxicity can be recognized at doses of nitroprusside exceeding 1.0 mg/kg (acutely administered). Accordingly, in the dogs studied at MAP 50 torr, the dose of nitroprusside was limited to a maximum of 1.0 mg/kg so as to be able to separate the effects of hypotension from those of cyanide toxicity.

The metabolic effects at 50 torr (equivalent to a cerebral perfusion pressure of 40 torr) were predictably less severe than those at 40 torr, and differences in cerebral effects among the four techniques were apparent. CMR_{O_2} was not decreased in any of the animals (except those given halothane), and cerebral lactic acidosis was apparent (but mild) only in the trimethaphan-treated animals. ATP was normal only in the halothane- and nitroprusside-treated animals. However, in all of the dogs, a slight hypoxia was suggested by reduction in PCr. This reduction could also be accounted for in part by a reduction in intracellular *p*H *per se*.[20] On balance, of the three clinically used techniques for inducing hypotension, trimethaphan would appear to be the least desirable in terms of the cerebral effects, which quantitatively were similar to those produced by hemorrhage. There was no difference between halothane- and nitroprusside-induced hypotension when the latter was associated with doses less than 1.0 mg/kg. These results are qualitatively compatible with those found by Yashon *et al.*[9] in comparing oligemia-, trimethaphan-, and halothane-induced hypotension in dogs at MAP 30–35 torr. At the end of an hour they found significantly greater cerebral lactic acidosis in oligemic and trimethaphan-treated animals than in halothane-treated animals. They did not examine nitroprusside-induced hypotension. Similarly, Magness *et al.*[10] reported results suggesting a possible direct toxic effect of trimethaphan on canine brain, and in that study (at MAP 30–47 torr), the cerebral effects of oligemic hypotension appeared to be less deleterious. It should be emphasized that the differences among hypotensive techniques observed in

the present study were apparent only at a cerebral perfusion pressure of 40 torr (not at 30 torr), and that these differences were quantitatively small and therefore of only questionable significance.

The near-uniform and significant metabolic abnormalities observed in all dogs maintained at MAP 40 torr (30 torr, cerebral perfusion pressure) for an hour were somewhat unexpected because of a significantly higher CBF maintained in the oligemic and nitroprusside-treated dogs (regardless of dose; table 6) compared with halothane- and trimethaphan-treated dogs. This suggested the possibility of non-homogeneous distribution of flow. However, no maldistribution of flow was observed in the brains of animals perfused with carbon black regardless of the technique used for inducing hypotension. This assumes that maldistribution would not be masked by nonpulsatile, postmortem perfusion. Thus, the explanation for similar metabolic derangements despite dissimilar flows remains unknown. Nonetheless, it seems appropriate to conclude that knowledge of CBF alone, in attempting to compare various techniques for inducing hypotension, is probably not sufficient for selecting a "preferred" technique.

The results in the ten animals observed for three days following hypotension demonstrated that the cerebral changes produced by an hour of hypotension at 40 torr (30 torr, cerebral perfusion pressure) may have important functional effects and are not consistently reversible. Three of ten animals made hypotensive with either halothane or trimethaphan (five dogs each) manifested persistent neurologic abnormalities during the period of observation. Again, there was a suggestion that trimethaphan effects were more deleterious, since two of the abnormal animals were given that drug, and one of them died during the second day of observation. We elected not to study oligemic and nitroprusside-treated animals in this manner since the former technique is clinically irrelevant and with the latter technique we were uncertain whether we could separate toxic effects of cyanide from the effects of hypotension *per se*.

The following conclusions appear justified. At very low perfusion pressures, the deleterious cerebral metabolic effects that occur are unaffected by the technique used for inducing hypotension or by differences in total flow to the brain. At marginal perfusion pressures, different hypotensive techniques may have different metabolic effects, such that either halothane- or nitroprusside-induced hypotension appears superior to that produced by trimethaphan or hemorrhage. Differences between techniques do not appear to be related to differences in distributions of flow to the brain. In dogs, nitroprusside acutely administered (*i.e.*, in one hour) produces direct toxic cerebral effects at total doses exceeding 1.0 mg/kg, and these effects are compatible with cyanide toxicity.

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