

Intracerebral Blood Flow Distribution during Hypotensive Anesthesia in the Goat

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The effects of hypotension (40–50 torr range) as induced by inhalation of halothane (2–3 per cent), halothane (0.75 per cent) plus sodium nitroprusside (0.2–0.4 mg/kg/min), or halothane (0.75 per cent) plus trimethaphan (4–16 mg/kg/min) on total and regional cerebral blood flow (tCBF, rCBF) in the goat were measured by radioactive microsphere distribution technique. Inhalation of halothane (2–3 per cent) alone caused an average reduction in tCBF of 25 per cent, with no significant reduction in regional flow except in cortical white matter, which showed a 42 per cent reduction. Halothane with sodium nitroprusside infusion caused an average 45 per cent decrease in tCBF and significant decreases in blood flows to the thalamus (42 per cent), cerebellum (41 per cent), cortical gray matter (35 per cent), and white matter (58 per cent). Halothane with trimethaphan infusion produced a reduction in tCBF (47 per cent), associated with significant decreases in blood flows to the thalamus (36 per cent), cerebellum (41 per cent), cortical gray matter (22 per cent), and white matter (47 per cent). Both halothane with sodium nitroprusside and halothane with trimethaphan produced significantly greater reductions of blood flows to the thalamus, cerebellum, and gray and white matter than did 2–3 per cent halothane. In addition, both caused significantly greater reductions in tCBF than did 2–3 per cent halothane. Of all the brain regions studied, only the hypophysis showed no statistically significant reduction in rCBF no matter which technique was used to produce hypotension. Conversely, cortical white matter appeared to be the region most affected by each technique. (Key words: Anesthetics, volatile: halothane. Anesthetic techniques, hypotension, induced: sodium nitroprusside. Blood pressure: hypotension. Brain: blood flow. Sympathetic nervous system: ganglionic blocking agents, trimethaphan.)

RECENT STUDIES concerned with hemodynamic changes associated with the deliberate induction of hypotension have appropriately focused on underperfusion of body organs as the primary danger associated with this technique.¹⁻² Reports comparing

the various techniques for inducing hypotension have consistently shown moderate, but presumably acceptable, reductions in cerebral blood flow (CBF) and other organs. However, as pointed out by Michenfelder *et al.*, a relatively high level of blood flow (at any reduced blood pressure) is no guarantee of adequate perfusion or of the absence of tissue hypoxia.² This point may have particular relevance with regard to the brain, where large differences in intracerebral regional blood flows have been demonstrated.³⁻⁵ Accordingly, the purpose of this study was to evaluate the impact of hypotension as induced by halothane, by halothane and sodium nitroprusside (SNP), or by halothane and trimethaphan (TM) on blood flows to different regions of the goat brain. For these purposes the distributions of radioactively labelled microspheres were studied before and after the induction of hypotension.

Methods

The study was performed with 28 adult female goats, 30–40 kg. Each was anesthetized with 1.5 per cent halothane in O₂ and placed upon a warming blanket to maintain body temperature at 38 C. Following this, the animal was paralyzed with pancuronium (0.05 mg/kg), the trachea intubated, and mechanical ventilation instituted. A thoracotomy was performed and an electromagnetic flow probe was placed around the pulmonary artery for measurement of cardiac output. Following this, a catheter was inserted into the left atrium for the injection of radioactively labelled microspheres. The thorax was then tightly sutured closed and the atrial catheter was externalized. Another catheter was inserted into the femoral artery for measurement of blood pressure and blood-gas determinations.

Upon completion of the surgical procedure the concentration of inspired halothane was reduced to approximately 0.75 per cent. Respiratory rate and volume were adjusted so that arterial blood CO₂ tensions (PaCO₂) were kept near normal. In the normal goat awake PaCO₂ is approximately 33 torr.⁶ After approximately 30 min at 0.75 per cent halothane, a bolus of ¹⁴¹Ce-labelled microspheres (15 ± 3 μm in diameter; 2.6 mCi/g)¶ was injected into the left atrium. In all cases

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¶ 3M Company, St. Paul, Minnesota 55101.

approximately 3×10^5 microspheres in 10 ml saline solution were injected. This was followed immediately by a 5-ml saline flush.

Following the first injection of microspheres, blood pressure was deliberately reduced to 40–50 torr by one of three techniques: high inspired halothane concentrations (2–3 per cent), low inspired halothane concentrations (0.75 per cent) with SNP infusion (0.2–0.4 mg/kg/min), or low inspired halothane concentrations (0.75 per cent) with TM infusion (4–16 mg/kg/min). After 30 min of hypotension, a bolus of ^{85}Sr -labelled microspheres ($15 \pm 3 \mu\text{m}$ in diameter; 2.7 mCi/g) was injected into the left atrium as previously described.

Ten minutes after the second injection of microspheres, the animal was sacrificed by injection of concentrated KCl. The skull was opened and the brain quickly removed and weighed. The brain was then bisected along its longitudinal axis. Portions of the thalamus, gray and white matters of the cerebral hemisphere, cerebellum, and hypophysis were removed from both halves of the brain. The weight of each sample was approximately 0.5–1.5 g. Sampling sites were located as indicated in figure 1. Techniques for removal of tissue have been described elsewhere.³ After the regional tissue samples were removed, the entire brain was homogenized in 200 ml of saline solution and aliquots of the suspension were transferred to vials for gamma scintillation counting. Regional tissue samples were also placed in vials for counting. The ^{141}Ce or ^{85}Sr activities in each sample were determined and differentiated as described by Hales.⁶

Total CBF and rCBF during normotension and hypotension were calculated from the total brain content of ^{141}Ce or ^{85}Sr , respectively, and cardiac output according to the formula:

$$t\text{CBF} = \text{CO} \times i\text{IBD}$$

where: CO = cardiac output in ml/min; iIBD = per cent of the total injected dose of microspheres found in the brain (or region). Throughout the entire procedure, cardiac output, arterial blood pressure, and blood-gas values were continuously monitored.

Cerebral vascular resistance (CVR) and total peripheral vascular resistance (TPVR) were calculated using the formula:

$$\text{TPVR (CVR)} = \frac{\text{mean arterial blood pressure (torr)}}{\text{cardiac output (CBF) in ml/min}}$$

where:

$$1 \text{ TPVR (CVR) unit} = \frac{1 \text{ torr}}{1 \text{ ml/min}}$$

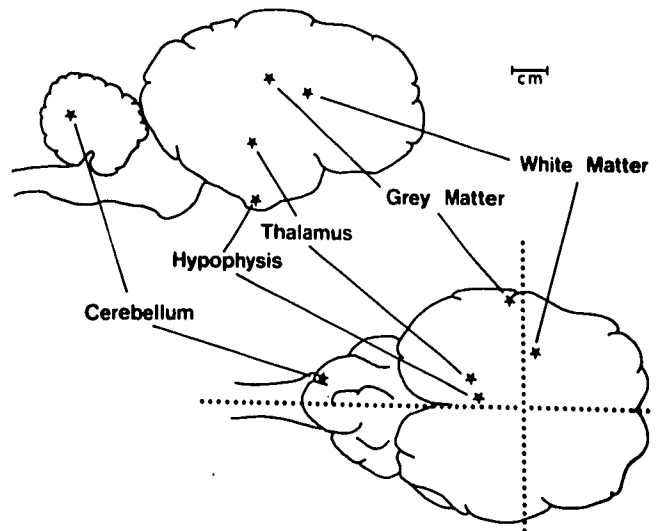


FIG. 1. Locations of tissue sampling sites for regional cerebral blood flow determinations. Samples were removed bilaterally for each tissue and blood flow rate results averaged.

Significance of differences was determined by the Student *t* test. In some instances, significance of differences was determined by one-way analysis of variance.

Results

Analysis of regional microsphere distribution during normotension and light halothane anesthesia revealed that the thalamus was the most highly perfused area studied (table 1). Parietal cerebral gray matter and the cerebellum were significantly less perfused than thalamic tissue. Cerebral white matter and the hypophysis were the least perfused regions studied.

High halothane concentrations (2–3 per cent) produced minimal reductions in all regions of the brain with the exception of cortical white matter. Halothane (0.75 per cent) and SNP (0.2–0.4 mg/kg/min) infusion resulted in reductions in blood flows to the gray and white matter of the cortex, cerebellum, and thalamus which were proportionate to the reduction in tCBF. Halothane (0.75 per cent) and TM (4–16 mg/kg/min) infusion produced results similar to those of halothane and SNP. Both halothane with SNP and halothane with TM produced significantly greater blood flow reductions to the thalamus, cerebellum, and gray and white matter compared with 2–3 per cent halothane. In addition, both caused significantly greater reductions in tCBF than did 2–3 per cent halothane.

Of all the brain regions studied, only the hypophysis was consistently resistant to blood flow reductions no matter which technique was used to produce

TABLE 1. The Effects of Hypotensive Anesthesia on Cerebral Blood Flow* and Cerebral Vascular Resistance†

	CVR	Total CBF	Gray Matter	White Matter	Thalamus	Hypophysis	Cerebellum
Halothane Normotension (n = 28)	1.82 ± 0.1	51 ± 5	40 ± 6	19 ± 2	53 ± 5	23 ± 3	46 ± 4
Hypotension (n = 9)	1.11 ± 0.03‡	38 ± 3(-25)‡	38 ± 5	11 ± 2(-42)‡	47 ± 3	24 ± 3	39 ± 6
Halothane + SNP Hypotension (n = 12)	1.5 ± 0.02§	28 ± 3(-45)§	26 ± 4(-35)§	8 ± 2(-58)‡	31 ± 4(-42)§	19 ± 3	27 ± 4(-41)§
Halothane + trimethaphan Hypotension (n = 7)	1.56 ± 0.01§	27 ± 2(-47)§	31 ± 2(-22)§	10 ± 2(-47)‡	34 ± 3(-36)§	16 ± 4	27 ± 4(-41)§

* Values represent mean ml flow per 100 g tissue ± SE.

† Values represent mean PRU ± SE (1 PRU = $\frac{1 \text{ torr}}{1 \text{ ml/min}}$).

‡ Significantly different from normotensive value, $P < 0.05$, significance determined by paired-data t test.

§ Region significantly different from halothane-induced hypotensive value, $P < 0.05$, significance determined by one-way analysis of variance.

Values in parentheses represent mean percentage decreases from normotensive values.

TABLE 2. Effects of Hypotensive Anesthesia on Cardiovascular Hemodynamics in the Goat (Mean ± SE)

	Mean Arterial Blood Pressure (torr)	Cardiac Output (ml/min)	Peripheral Vascular Resistance (Units × 10 ⁻³)	Per Cent Cardiac Output Perfusing Brain	P _{aCO₂} (torr)
Halothane Normotension (0.75 per cent; n = 28)	93 ± 4	2312 ± 842	3.89 ± 1.38	2.2 ± 0.25	35 ± 4
Hypotension (2-3 per cent; n = 9)	42 ± 2*	1287 ± 383*	3.26 ± 0.86*	3.0 ± 0.6*	34 ± 3
Halothane (0.75 per cent) + SNP Hypotension (n = 12)	44 ± 4*	1491 ± 790*	3.01 ± 1.86*	1.9 ± 1.1	34 ± 4
Halothane (0.75 per cent) + trimethaphan Hypotension (n = 7)	42 ± 3*	1683 ± 884*	2.79 ± 1.49*	1.6 ± 1.0	32 ± 3

* Significant difference from normotensive values, $P < 0.05$, significance determined by paired-data t test.

hypotension. At the other extreme, cortical white matter consistently showed the largest reduction in blood flow with all hypotensive methods.

For approximately equal reductions in mean arterial blood pressure, the three techniques produced approximately equivalent reductions in cardiac output (table 2). Cerebral vascular resistance and TPVR were significantly reduced by all techniques (tables 1 and 2), compared with normotensive values. Halothane, 2-3 per cent, caused a significantly greater reduction in CVR than did halothane, 0.75 per cent in combination with SNP or TM. The percentage of cardiac output perfusing the brain was significantly increased during hypotension produced by halothane (2-3 per cent) inhalation but not during that found with SNP or TM infusion (table 2).

Discussion

The results of this study confirm previous reports that the brain contains discrete regions of disparate blood flows.³⁻⁵ That this observation may have im-

portant implications regarding intracerebral blood flow during hypotension can be readily appreciated upon examination of regional flow changes associated with blood pressure reduction. When blood pressure was reduced to a mean of 40-50 torr with halothane anesthesia, tCBF decreased only 25 per cent, but flow to the white matter of the cerebral hemisphere was reduced 42 per cent. Since blood flows to other sampled areas of the brain were not significantly affected, it would seem that the decrease in tCBF occurred primarily at the expense of cortical white matter. This suggests that severe reductions in tCBF during "deep" halothane anesthesia might result in underperfusion of white matter of the cerebral cortices.

Hypotension produced by low halothane concentrations and SNP, or by low halothane concentrations and TM, resulted in rCBF changes that differed from those changes caused by halothane alone. Both SNP and TM produced significantly greater reductions in tCBF. In addition, these agents caused reductions in the sampled portions of the cerebellum,

thalamus, cortical gray matter, and cortical white matter that were more or less proportionate to the reductions seen in tCBF. Despite significant declines in blood flows to these other areas of the brain, cortical white matter declined to an even larger extent in both instances. This, again, indicates that cerebral cortical white matter may be particularly susceptible to underperfusion during hypotension.

In contradistinction to the latter observation, it was found that, of the five brain regions studied, only the hypophysis appeared to maintain normotensive blood flow in the face of hypotension as caused by all three techniques. This is surprising in that under normotensive conditions the hypophysis ranked with cortical white matter as the least perfused region of the brain. That the hypophysis maintained normal blood flow during hypotension while cortical white matter did not suggests the interesting possibility that certain regions of the brain may autoregulate their respective blood flows.

Of the three techniques studied, administration of high halothane concentrations had the least effect on tCBF and rCBF. However, the three methods produced approximately equal reductions in cardiac output. It is evident, therefore, that the percentage of cardiac output perfusing the brain in the halothane group increased during hypotension. This could be accomplished only by a proportionate decrease in cerebral vascular resistance, and suggests that high halothane concentrations had much less effect on cerebral autoregulation of blood flow than did the other two techniques. Recent reports from our laboratory and others showed, however, that halothane in clinically useful dosages abolished autoregulation.^{7,8} This variance may be explained by unpublished observations from our laboratory. Recent work has shown us that after prolonged (two hours) exposure to 1 per cent halothane, autoregulation is about 80 per cent restored, and tCBF returns to pre-inhalation levels. Because CBF measurements in the present study were made after lengthy (1–1.5 hours) surgical manipulations, presumably enough time elapsed for the possible return of autoregulation in those animals treated with halothane only. However, it would seem that vasoactive agents such as SNP and TM antagonize the restoration of autoregulation, since the animals in these groups had greater reductions in tCBF. Sodium nitroprusside has been shown to cause a loss of autoregulation in awake goats and anesthetized monkeys.^{9,10} Stoyka and Schutz, however, reported "presumptive evidence" that SNP did not abolish cerebral autoregulation in the thio-pental-ketamine-anesthetized dog.¹¹ In their study

CBF remained nearly constant while blood pressure and cardiac output decreased due to SNP infusion. Apparently, these investigators considered their evidence presumptive, since they did not actually challenge cerebral autoregulation during SNP treatment with a rapid increase in peripheral blood pressure such as might be induced with a bolus of angiotensin. In order to prove the absence or presence of autoregulation, a maneuver like this is essential. Autoregulation of blood flow by any organ is thought to be an active process. Testing autoregulation with a passive decreasing peripheral pressure challenge is only a partial test. This explanation may also apply to the work of Fitch *et al.*, in which SNP was thought not to have impaired cerebral autoregulation in the baboon.¹² It is not clear from this study whether cerebral autoregulation was challenged with a pressor test.

A possible weakness in this study is that "control" values, *i.e.*, CBF before the induction of hypotension, were obtained while the animals were breathing 0.75 per cent halothane in oxygen. However, regional blood flows seen under these conditions compare reasonably well to relative regional flow distributions reported by us for the awake goat.³

An additional caveat to the interpretation of the data in this study is that only small areas of each region were studied and compared. Since large inclusive regions such as cerebral gray and white matter are in themselves heterogeneously perfused, the areas selected for study may not reflect total grey or white matter blood flow during normotension and hypotension.

Finally, it is known that autoregulation of CBF may be lost in cerebrally traumatized or diseased patients.^{13,14} Measurements of tCBF and rCBF in normal animals might not accurately reflect the potential problems presented by such patients. It is possible that differences in rCBF during hypotension may have even graver implications for the impaired patient.

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