Blood Flow Distribution and Brain Metabolism during Tolazoline-Induced Hypotension in Newborn Dogs

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ABSTRACT. Tolazoline is used in neonatal intensive care to treat hypoxia secondary to persistent pulmonary hypertension of the newborn. Its use is often complicated by systemic hypotension. We compared the effect of tolazoline-induced hypotension on organ blood flow, regional brain blood flow, and cerebral metabolism in hypoxic newborn dogs whose mean arterial pressure fell by more than 20% with a second group whose blood pressure fell by less than 20%. Blood flows were measured by the radioactive microsphere technique. We found no changes in organ blood flow, regional brain blood flow, and cerebral metabolism in hypoxic animals whose mean arterial blood pressure decreased less than 20% during tolazoline administration. However, in those animals whose mean arterial blood pressure decreased more than 20%, we found a decrease in cerebral blood flow. As a consequence of decreased cerebral blood flow, cerebral oxygen delivery decreased. However, oxygen extraction increased so that cerebral metabolic rate was preserved. (*Pediatr Res* 28: 111-115, 1990)

Abbreviations

PaO₂, arterial O₂ tension
PaCO₂, arterial CO₂ tension

hypoxia interferes with cerebral autoregulation, then concomitant systemic hypotension could diminish brain blood flow. Therefore, this experiment was performed to find if tolazoline-induced hypotension decreased or changed the regional distribution of brain blood flow during hypoxia, and whether such changes affected brain oxygen delivery or brain metabolism.

MATERIALS AND METHODS

Animals. Twenty mongrel dogs age 7 to 13 d were used for these studies. The experimental protocol was approved by the Animal Care and Use Committee of Magee-Womens Hospital. Each animal was placed on a warming mattress and its temperature was monitored with a rectal temperature probe. After the animal had been anesthetized with 4% halothane, we placed a femoral venous catheter (for tolazoline administration) and two femoral arterial catheters, positioned above the aortic bifurcation and below the renal arteries (one for continuous blood pressure monitoring and one for access to arterial blood and reference sample withdrawals during microsphere injections). A catheter was also placed in the left ventricle via the ligated left common carotid artery (for microsphere injections). Finally, we placed a catheter through the anterior skull into the sagittal sinus to obtain blood samples from the venous drainage of the brain.

Experimental protocol. We allowed the animals 90 min to recover from anesthesia, then obtained blood for arterial and sagittal sinus blood gases, Hb, and hematocrit determinations. Blood flow was measured by injection of radiolabeled microspheres and withdrawal of a reference blood flow sample (4). We replaced all blood withdrawn with an equal volume of blood obtained from a littermate. The animals were then placed in a hypoxic environment (9% oxygen, 2 to 6% carbon dioxide, the balance nitrogen). We measured arterial blood gases intermittently and changed the carbon dioxide content of the gas mixture to keep PaCO₂ constant. After 45 min, we repeated the blood gas, Hb, hematocrit, and blood flow measurements. Next, we administered sufficient tolazoline hydrochloride (Priscoline Hydrochloride, CIBA Pharmaceutical Co., Summit, NJ) to the animals to decrease mean arterial blood pressure by more than 20% of its value during the preceding period of hypoxia (group 1 animals) or less than 20% of its value during hypoxia (group 2 animals). We then began a constant infusion of tolazoline at a rate of 2 mg/kg of body wt/h. After 45 min of tolazoline administration, we obtained a 3rd set of arterial and sagittal sinus blood samples and measured blood flow again. We killed the animals by injection of euthanasia solution, verified all catheter positions at autopsy, and removed and weighed the organs. The brain was

Pulmonary vascular resistance, which is relatively high *in utero*, usually declines abruptly after birth. However, in a variety of clinical settings, pulmonary vascular resistance does not fall, thereby causing high pulmonary artery pressures, right to left shunting of blood across the foramen ovale or ductus arteriosus and attendant systemic hypoxemia. Tolazoline, which has a complex action on smooth muscle, including α -adrenergic blockade, has been used as a putative pulmonary vasodilator. Unfortunately, tolazoline also has effects on systemic vascular resistance, and a serious side effect of its use is systemic hypotension (1).

The maintenance of blood flow to an organ despite fluctuations in systemic blood pressure has been termed autoregulation (2). Lou *et al.* (3) have suggested that hypoxic newborns have an impairment of normal autoregulation of brain blood flow. If

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Table 1. Mean arterial blood pressure, heart rate, pH, blood gas, and hematocrit (means $\pm$ SEM)

	Group 1 (n = 10)			Group 2 (n = 10)		
	Initial	Hypoxia	Hypoxia + tolazoline	Initial	Hypoxia	Hypoxia + tolazoline
Mean arterial blood pressure (mm Hg)	60 $\pm$ 3	62 $\pm$ 5†	43 $\pm$ 4*	61 $\pm$ 3	65 $\pm$ 2	57 $\pm$ 2*
Heart rate (beats/min)	247 $\pm$ 8	231 $\pm$ 11	224 $\pm$ 6	244 $\pm$ 3	226 $\pm$ 6*	219 $\pm$ 7
pH	7.40 $\pm$ 0.03	7.25 $\pm$ 0.02*	7.18 $\pm$ 0.03*	7.49 $\pm$ 0.04	7.33 $\pm$ 0.05*	7.20 $\pm$ 0.04*
Pao ₂ (torr)	90 $\pm$ 6	34 $\pm$ 2*	36 $\pm$ 2	90 $\pm$ 5	35 $\pm$ 2*	39 $\pm$ 2
Paco ₂ (torr)	34 $\pm$ 3	36 $\pm$ 2	34 $\pm$ 1	26 $\pm$ 3	31 $\pm$ 3	30 $\pm$ 2
Hematocrit (%)	36 $\pm$ 1	34 $\pm$ 2*	32 $\pm$ 2*	36 $\pm$ 2	34 $\pm$ 2*	32 $\pm$ 2*

* $p < 0.05$ compared to previous value within group.

† $p < 0.01$ compared to percent change between the same conditions in group 2.

Table 2. Organ blood flows expressed as mL/min/100 g of tissue (means $\pm$ SEM)

	Group 1 (n = 10)			Group 2 (n = 10)		
	Initial	Hypoxia	Hypoxia + tolazoline	Initial	Hypoxia	Hypoxia + tolazoline
Heart	207 $\pm$ 29	288 $\pm$ 45	317 $\pm$ 39	218 $\pm$ 35	253 $\pm$ 13	314 $\pm$ 33
Liver (hepatic artery only)	24 $\pm$ 5	34 $\pm$ 6*	38 $\pm$ 8	24 $\pm$ 5	36 $\pm$ 6*	37 $\pm$ 5
Gastrointestinal tract	61 $\pm$ 8	49 $\pm$ 4	82 $\pm$ 10*	61 $\pm$ 7	63 $\pm$ 12	63 $\pm$ 4
Spleen	124 $\pm$ 16	91 $\pm$ 8	95 $\pm$ 8	131 $\pm$ 25	139 $\pm$ 28	109 $\pm$ 15
Right kidney	100 $\pm$ 15	92 $\pm$ 13	94 $\pm$ 8	118 $\pm$ 23	116 $\pm$ 16	114 $\pm$ 13
Left kidney	109 $\pm$ 17	92 $\pm$ 10	100 $\pm$ 8	117 $\pm$ 24	122 $\pm$ 20	116 $\pm$ 15
Carcass	19 $\pm$ 3	17 $\pm$ 4	16 $\pm$ 2	19 $\pm$ 5	16 $\pm$ 2	12 $\pm$ 1*
Brain	39 $\pm$ 5	65 $\pm$ 5*†	50 $\pm$ 5*	38 $\pm$ 5	59 $\pm$ 5*	64 $\pm$ 6
Cardiac output	262 $\pm$ 28	253 $\pm$ 31	269 $\pm$ 25	300 $\pm$ 54	272 $\pm$ 37	243 $\pm$ 16

* $p < 0.05$ compared to previous value within group.

† $p < 0.05$ compared to percent change between the same conditions in group 2.

removed, fixed in 10% formaldehyde, then dissected and weighed.

Measurements. Throughout the study, we measured arterial blood pressure with a Statham (Cambridge, MA) P23Db pressure transducer connected to one hind limb arterial catheter. Heart rate was obtained from a cardiometer coupled to the blood pressure channel. Both measurements were recorded continuously on a Beckman (Schiller Park, IL) R511A direct writing recorder. We measured arterial blood gases and pH on a Corning blood gas meter (model no. 168, Corning Instruments, Corning, NY). Blood Hb content and the percent saturation with oxygen were measured with a hemoximeter (OSM2 Hemoximeter, Radiometer, Copenhagen, Denmark). The blood oxygen content (mmol/mL) was then calculated as:

$$\begin{aligned} \text{O}_2 \text{ content (mmol/mL)} &= (1.34 \times \text{g Hb}/100 \text{ mL} \\ &\times \% \text{ Hb saturation} + 0.003 \times \text{Pao}_2) \\ &\times (1 \text{ mmol O}_2/22.39 \text{ mL O}_2) \end{aligned}$$

Hematocrits were measured by the microhematocrit method. Blood flow determinations were performed by the radioactive microsphere method (4). Microspheres (15- μ m diameter) labeled with ⁴⁶Sc, ⁵¹Cr, ⁸⁵Sr, or ¹⁴¹Ce (New England Nuclear, Boston, MA) were injected into the left ventricular catheter over a 10-s period. A blood reference sample was withdrawn concurrently at a rate of 4 mL/min from a hind limb arterial catheter using a withdrawal pump beginning before the microsphere injection and ending 60 s after the injection catheter was flushed with saline. No changes in mean arterial pressures were noted secondary to microsphere injections. Sampling and microsphere injections were accomplished within 5 min. Preliminary data indicated that approximately 10⁶ microspheres per injection were required to ensure a reference arterial blood flow measurement error of less than 5% at the 95% confidence limits and to provide sufficient particles and radioactivity to accurately assess individual organ and segmental brain blood flows (5).

At the end of each experiment, the weighed tissues were incinerated at 280°C for 72 h, after which the ash was packed in counting vials. The amounts of each radionuclide in the organs and the reference arterial blood samples were measured with a well-type gamma scintillation counter (Model 1185R, Searle Analytical, Des Plaines, IL) with a 1024 channel pulse height analyzer (Ultima II, Norland Instruments, Ft. Atkinson, WI). Nucleotide isotope separation was performed by a computer (Nova 3; Data General, Southboro, MA) using a previously verified program. Organ blood flow is computed as follows:

$$Q_{\text{organ}} = (\text{CPM}_{\text{org}}/\text{CPM}_{\text{ref}}) \times (Q_{\text{ref}})$$

where CPM_{org} is the radioactive cpm in the organ, CPM_{ref} is the radioactive cpm in the reference arterial blood sample, and Q_{ref} is the reference arterial blood flow determined by calibrating the withdrawal pump. Cardiac output is the sum of all organ and carcass flows. Flows per unit wt were calculated by dividing the organ flow (mL/min) by the tissue wt (in 100 g).

Brain oxygen delivery (mmol/min/100 g tissue) is:

$$\text{O}_2 \text{ del} = Q_{\text{brain}} \times [\text{O}_2]_a$$

where Q_{brain} is brain blood flow (mL/min/100 g tissue) and [O₂]_a is arterial oxygen content (mmol/mL).

Brain oxygen consumption (mmol/min/100 g tissue) is:

$$\text{O}_2 \text{ cons} = Q_{\text{brain}} \times ([\text{O}_2]_a - [\text{O}_2]_v)$$

where [O₂]_v is sagittal sinus oxygen content (mmol/mL) and Q_{brain} and [O₂]_a are as defined above. Brain fractional oxygen extraction is:

$$\text{O}_2 \text{ ext} = \frac{\text{O}_2 \text{ cons}}{\text{O}_2 \text{ del}} = \frac{[\text{O}_2]_a - [\text{O}_2]_v}{[\text{O}_2]_a}$$

Data analysis. We used paired and unpaired *t* tests with the Bonferroni correction procedure for multiple comparisons to compare the mean percent changes in physiologic parameters.

Fig. 1. Regional brain blood flow during initial conditions, hypoxia, and hypoxia plus tolazoline infusion. A) cerebellar blood flow, B) brain stem blood flow, C) thalamic blood flow, D) cerebral cortical blood flow, and E) cerebral white matter blood flow. Broken line represents group 1 animals (decrease in mean arterial pressure >20%), $n = 10$. Solid line represents group 2 animals (decrease in mean arterial pressure <20%), $n = 10$. Values shown are means $\pm$ SEM. * $p < 0.05$, comparing mean percent change between the two groups.

tissue blood flows, and brain oxygen deliveries, consumptions, and extractions between experimental conditions for the two groups of animals. All data are presented as group means $\pm$ SEM.

RESULTS

Animals whose mean arterial blood pressure fell during hypoxia and tolazoline infusion by greater than 20% (group 1) were compared with those whose pressure fell by less than 20% (group 2) so that we could study the effects of tolazoline-induced hypotension during hypoxia. Table 1 shows that, although no blood pressure changes occurred in either group during hypoxia, after 45 min of tolazoline infusion during hypoxia, blood pressure

Fig. 2. Regional brain blood flow during initial conditions, hypoxia, and hypoxia plus tolazoline infusion. A) right cerebral cortical blood flow and B) left cerebral cortical blood flow. Broken line represents group 1 animals (decrease in mean arterial pressure >20%), $n = 10$. Solid line represents group 2 animals (decrease in mean arterial pressure <20%), $n = 10$. Values shown are means $\pm$ SEM. * $p < 0.05$, comparing mean percent change between the two groups.

had fallen in group 1 animals ($n = 10$) by $32 \pm 3\%$ (range = 20–46%), whereas a $12 \pm 2\%$ decrease (range = 0–18%) occurred in group 2 animals ($n = 10$). The dose of tolazoline used in group 1 animals (7.0 ± 1.2 mg/kg) was not different ($p = 0.45$) from that received by those in group 2 (8.3 ± 1.2 mg/kg).

Heart rate decreased in group 2 during hypoxia and then remained stable. The pH and hematocrit fell through the experiment in both groups. P_{aCO_2} remained stable during the experiment within groups. There were no statistical differences between groups for percent changes in heart rate, pH, P_{aO_2} , P_{aCO_2} , or hematocrit between conditions throughout the experiment.

Data concerning organ blood flows are shown in Table 2. Percent changes in myocardial, hepatic arterial, splenic, and renal flows between conditions were not different between groups. Right and left renal flows were not different within or between groups. Changes in carcass blood flow were not different between

Fig. 3. Brain oxygen delivery, consumption, and extraction during initial conditions, hypoxia, and hypoxia plus tolazoline infusion. A) brain oxygen delivery, B) brain oxygen consumption, and C) brain oxygen extraction. Broken line represents group 1 animals (decrease in mean arterial pressure $>20\%$), $n = 10$. Solid line represents group 2 animals (decrease in mean arterial pressure $<20\%$), $n = 10$. Values shown are means $\pm$ SEM. * $p < 0.05$, comparing mean percent change between the two groups.

groups. Cardiac output did not change throughout the experiment in either group.

Gastrointestinal blood flow rose in group 1 animals between conditions of hypoxia plus tolazoline administration. However, there was no difference between the two groups in the mean percent change in gastrointestinal blood flow between these conditions ($p = 0.054$). The lack of a difference between the two groups of animals in this regard indicates that factors other than tolazoline-induced hypotension are responsible and suggests that this finding is of questionable significance.

The most striking findings are those related to brain blood flow. During hypoxia, brain blood flow increased by $87 \pm 21\%$ in group 1 and by $82 \pm 28\%$ in group 2. During tolazoline infusion, brain blood flow fell by $20 \pm 7\%$ in group 1 and did

not change ($10 \pm 10\%$) in group 2 (difference between groups $p < 0.05$).

Regional brain blood flow data are shown in Figure 1. During hypoxia, blood flow rose in all brain regions in both groups. Changes in blood flows to the cerebellum, brain stem, and thalamus during the experiment were not different between the two groups of animals. However, during tolazoline infusion, cerebral flow decreased by $32 \pm 6\%$ in group 1 but did not change ($-2 \pm 8\%$) in group 2 (difference between groups $p < 0.01$). Cerebral white matter blood flow exhibited a similar pattern, i.e. flow decreased during tolazoline administration by $31 \pm 7\%$ in group 1 but did not change ($6 \pm 11\%$) in group 2 (difference between groups $p < 0.01$).

To examine the effect of left carotid artery ligation on the experimental results, we compared right and left cerebral blood flows (Fig. 2). Although we did observe a greater decrease in left cerebral cortex blood flow than that seen on the right during tolazoline-induced hypotension and hypoxia (43 versus 20% decrease, $p < 0.01$), the patterns of changes in blood flows in the two cerebral hemispheres are the same as those in the cerebrum as a whole.

Figure 3 shows the data for brain metabolism. Brain oxygen delivery was maintained during hypoxia in both groups (Fig. 2A) but fell by $31 \pm 7\%$ in group 1 during tolazoline infusion compared with no change ($-6 \pm 5\%$) in group 2 ($p < 0.02$). O₂ consumption (Fig. 2B) remained stable during hypoxia and did not change significantly during tolazoline infusion because oxygen extraction (Fig. 2C) rose by $33 \pm 10\%$ during tolazoline infusion in group 1, whereas it did not change ($6 \pm 5\%$) in group 2 ($p < 0.05$).

DISCUSSION

We designed this experiment to define the relationship between tolazoline-induced systemic hypotension during hypoxia and organ blood flow. During tolazoline-induced hypotension in hypoxic newborn dogs, we found a decrease in cerebral blood flow. The precise mechanism responsible for this decrease in cerebral blood flow without dramatic changes in other organ blood flows is unclear. Gregory *et al.* (6), in a study of the effects of tolazoline on the distribution of cardiac output in normoxemic and hypoxemic lambs, found increases in cardiac output and brain blood flow during hypoxia that were preserved during the administration of varying doses of tolazoline. They observed no differences in abdominal visceral blood flows between periods of normoxemia, hypoxemia, and hypoxemia with concomitant tolazoline administration. However, the total dose of tolazoline administered in their study (5 mg/kg) was lower, as was the decrement in blood pressure (8%), than that observed in our study.

The major pharmacologic action of tolazoline is direct vasodilation. However, sympathomimetic, parasympathomimetic, histamine-like, and α -adrenergic blocking activities have been described. The α -adrenergic blocking actions of tolazoline are thought to predominate at higher doses of the drug such as those used in our study (1). Weiss and Buchweitz-Milton (7), in a study of the role of α -adrenoceptors in the control of the cerebral blood flow response to hypoxia in rabbits, showed that α -adrenoceptor antagonism by phenoxybenzamine significantly attenuated the increase in cerebral blood flow produced by hypoxia. We speculate that α -adrenergic blockage secondary to tolazoline would also lead to an inhibition of peripheral arteriolar vasoconstriction, especially of the abdominal viscera. This would tend to preserve, or even increase, peripheral organ blood flow despite a decrease in perfusion pressure. It is tempting to invoke variability in the degree of α -adrenergic blockade despite equivalent doses of tolazoline to explain the differences in blood pressure responses we observed between the two groups of animals.

A second purpose of this experiment was to examine the effect of hypoxia and subsequent tolazoline-induced systemic hypoten-

sion during hypoxia on cerebral blood flow and metabolism. We noted marked increases in total and regional brain blood flows during hypoxia in this experiment between baseline and hypoxic conditions. These findings agree with previous studies in numerous species including the newborn dog (8).

Laptook and Rosenfeld (9) studied the cerebral vascular response to tolazoline infusion in the hypoxic piglet and found no changes in cerebral blood flow or cerebral O₂ delivery, extraction, or consumption after tolazoline administration. However, they noted that cerebral blood flow was variable during tolazoline exposure, decreasing in four of 10 piglets. These reductions in cerebral blood flow were associated with decreases in mean arterial pressure. We chose a tolazoline-induced blood pressure change of 20%, based on Laptook and Rosenfeld's data, as a "threshold" level of hypotension. We administered sufficient amounts of tolazoline to achieve a mean fall in blood pressure of approximately 20% in the experimental animals, with half of the subjects falling above and half below the targeted 20% change in mean arterial blood pressure.

In our study, we have demonstrated that tolazoline-induced hypotension in the hypoxic newborn dog decreases brain blood flow and changes its distribution, thereby adversely affecting brain oxygen delivery. Our data agrees with that of Laptook and Rosenfeld (9) in that we found no changes in cerebral blood flow or cerebral O₂ delivery, consumption, or extraction during tolazoline infusion in animals whose mean arterial blood pressure decreased by less than 20%. In contrast, those animals who did develop a greater than 20% decrease in mean arterial pressure exhibited decreased cerebral blood flow and cerebral O₂ delivery. In this situation, O₂ extraction rose, presumably in response to decreased cerebral O₂ delivery. This increase in O₂ extraction tended to offset the observed decrease in O₂ delivery, thereby maintaining cerebral O₂ consumption and cerebral metabolic function.

Other factors influence cerebral blood flow and cerebral metabolism. Although changes in PaO₂, PaCO₂, and hematocrit have profound effects on brain blood flow (8), none of these variables was different between the two groups in this study. Vannucci *et al.* (10) have found that carotid artery ligation (secondary to the placement of a left ventricular catheter via the carotid artery) could adversely affect cerebral blood flow during hypoxia. However, such changes in blood flow secondary to instrumentation could not explain the differences we observed between group 1 and group 2 animals, inasmuch as the animals in these groups were prepared identically.

The differences in regional brain blood flow we observed during tolazoline-induced hypotension are similar to those described previously during hypotension induced by experimental hemorrhage. During normoxia in newborn piglets, reductions of blood flow are most pronounced in the cerebrum, less in the cerebellum, and least in the brainstem when severe systemic hypotension is produced by intravascular depletion (11, 12).

Young *et al.* (13) have reported a selective reduction of blood flow to the cerebral white matter during normoxia and hemorrhagic hypotension in the newborn dog. In contrast, cerebral white matter flows were not affected more than general cerebral blood flow in our experiment. This difference may be attributable to dissimilarity in blood flow patterns produced by hypotension with concomitant hypoxia and hypotension without hypoxia.

Klesh *et al.* (14) reported a 47% incidence of cerebral infarction in a cohort of severely asphyxiated infants who developed persistent pulmonary hypertension of the newborn. Tolazoline therapy was used in 84% of these infants, and 32% required dopamine hydrochloride infusions in addition to i.v. volume expansion to maintain an adequate systemic blood pressure. We speculate that tolazoline-induced hypotension decreases cerebral blood flow in sick infants at a time when cerebral blood flow should be maximal to maintain adequate O₂ delivery for normal cerebral metabolism. Under such conditions, decreased cerebral blood flow would predispose these infants to adverse changes in cerebral metabolism and an increased risk of hypoxic-ischemic cerebral damage.

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