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Responses of Newborn Pig Pial Arteries to Sympathetic Nervous Stimulation and Exogenous Norepinephrine

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ABSTRACT. The purpose of this study was to examine responses of pial arteries of newborn pigs to stimulation of sympathetic nerves and to exogenous norepinephrine. In the cerebral circulation, pial arteries are important resistance vessels. Diameters of pial arteries in anesthetized piglets, aged 1–6 days, were determined using the "closed" cranial window method. Electrical stimulation of the ipsilateral superior cervical ganglion (16 Hz; 2.5 msec; 10 V) reduced pial arterial diameter from 219 ± 13 μm (mean ± SEM) to 190 ± 12 μm ($n = 16$) ($p < 0.05$) without affecting arterial blood pressure. Pial arterial constriction during nerve stimulation was sustained over the 5-min stimulation period. Following cessation of stimulation, diameters returned to control levels. Exogenous norepinephrine in artificial cerebrospinal fluid constricted pial arteries from 149 ± 19 to 133 ± 18 μm at 2×10^{-6} M ($p < 0.05$) and from 159 ± 20 to 123 ± 16 μm at 2×10^{-4} M ($p < 0.05$) (18 arteries from nine piglets). Pial arterial responses to nerve stimulation and exogenous norepinephrine were not dependent on initial size of the vessels. The results of this study establish the existence of functional sympathetic innervation in the cerebral circulation at birth in pigs. (*Pediatr Res* 19: 1210–1214, 1985)

Abbreviations

CBF, cerebral blood flow
CSF, cerebrospinal fluid

The sympathetic nervous system plays an important role in regulation of the cerebral circulation and development of cerebral arteries (1). However, functional sympathetic innervation of cerebral vessels of the adult pattern may not be completed at birth but may develop over the following days or weeks. For example, complete anatomical development of sympathetic innervation of mice cerebral vessels does not take place until 3–4 wk after birth (2). Similar developmental changes in terms of physiological function take place in the heart (3) and in other regional circulations (4).

Although anatomical development of sympathetic innervation may not be completed at birth, cerebral arteries of newborns still could respond to adrenergic stimuli. However, only a few studies have examined effects of sympathetic nervous stimulation and of α-adrenergic agents on cerebral arteries. Wagerle *et al.* (5) have shown that electrical stimulation of sympathetic nerves reduces CBF in newborn lambs. In addition, Hernandez *et al.* (6) reported that reflex activation of sympathetic nerves during severe asphyxia caused vasoconstriction in forebrain structures of newborn puppies. Recently, Hayashi *et al.* (7) showed that isolated cerebral arteries from the baboon fetus and newborn constricted in response to exogenous norepinephrine and phenylephrine.

Previous studies on other regional circulations indicate that, in newborn animals, vascular responsiveness to nerve stimulation and exogenous norepinephrine may or may not develop simultaneously. On one hand, the renal circulation of newborn swine is relatively sensitive to nerve stimulation and exogenous norepinephrine (4). In contrast, the femoral circulation of newborn swine is not consistently responsive to exogenous norepinephrine but is responsive to sympathetic nervous stimulation (4). The correspondence between responsiveness to sympathetic nerve stimulation and exogenous norepinephrine has not been examined before in the newborn cerebral circulation.

The purpose of this study was to examine adrenergic mechanisms in the cerebral circulation of newborn pigs. We tested the hypothesis that sympathetic nerve stimulation and exogenous norepinephrine would constrict cerebral arteries.

METHODS

Twenty newborn pigs (0.4–2.5 kg) of either sex, aged 1–6 days, were used in these experiments. They were anesthetized initially with ketamine hydrochloride (33 mg/kg, intramuscular) and acepromazine or xylazine (3.3 mg/kg, intramuscular). Anesthesia was maintained with α-chloralose (30–50 mg/kg, intravenous). α-Chloralose was used because the level of achieved anesthesia was consistent with government guidelines for studying animals and because previous studies indicate that α-chloralose has minimal effects on the peripheral circulation compared to other anesthetic agents (8). The animals were intubated and ventilated with air and supplemental O_2. A catheter was inserted into a femoral vein for injection of drugs and fluids, and another catheter was inserted into a femoral artery to record blood pressure and to sample for blood gases and pH. Temperature was maintained at 37–39° C with a heating pad.

Cranial Window Method. The scalp was removed from both sides of the head, and a burr hole, approximately 2 cm in diameter, was made in the skull over the parietal cortex with bone rongeurs. The dura was cut and reflected over the bone. A cranial window, similar to that described by Levasseur *et al.* (9),

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was placed into the hole and cemented into place with dental acrylic. After the dental acrylic hardened, the space under the window was filled with artificial CSF. The composition of the CSF was the same as that used by Levasseur *et al.* (9). Artificial CSF was maintained at the animal's body temperature before injection using a heated water bath. Preliminary experiments, described below, indicated that this CSF was suitable for use in our studies on piglets. Following implantation of the window, we waited for at least 30 min before continuing the experiments.

Pial arteries were observed with a Wild M7S trinocular stereomicroscope. Vessel width was measured using a television camera (model VC-65SL, Dage-MIT, Michigan City, IN) mounted on the microscope, a video monitor (model CT-1930V, Panasonic Corp., Secaucus, NJ), and a video Micro-Scaler (model VPA-1000, For-A-Corp., Los Angeles, CA). To make our measurements, a magnified image of the pial arteries was displayed on the video monitor. The Micro-Scaler generates two parallel lines on the monitor, and these are independently controlled, and one line is positioned on each side of the vessel. The distance between the lines is precalibrated with a stage micrometer. We have determined that the scaler was linear over the range from 0 to 1000 μm. By rotating the television camera, it is possible to make measurements of several vessels of different diameters.

We initially assessed effects of the artificial CSF on piglet pial arteries. In all experiments described herein, the artificial CSF contained ascorbic acid (500 μg/ml CSF) as an antioxidant. After the initial flushing the of window with CSF, we waited at least 30 min for the injected CSF to become equilibrated with endogenous cerebral extracellular fluids. At that time, arterial diameters were measured. Then, artificial CF again was infused under the window, and diameters measured after 1–3 min. The mean ± SEM for the first measurement was 163 ± 16 μm and the value for the second measurement was 166 ± 17 μm (NS; 21 arteries from 11 animals). The correlation coefficient for the two values was 0.99 ($p < 0.05$). Thus, the composition of the artificial CSF used was suitable in that replacement of CSF composed primarily of endogenous CSF (30 min after flushing with artificial CSF) with new artificial CSF did not alter pial arterial diameters.

Experimental Protocols.

Effects of sympathetic stimulation. In 16 piglets, pial arterial diameters were measured during a prestimulation period and every minute over a 5-min stimulation period (16 Hz; 2.5 msec; 10 V). A midline incision was made over the trachea and the left superior cervical ganglion was isolated near the carotid artery using a ventral approach. Bipolar stimulating electrodes were placed around the preganglionic fibers supplying the superior cervical ganglion or around the caudal end of the ganglion. The initial artery sizes ranged from 163–309 μm in diameter. Diameters also were measured 5–10 min following cessation of stimulation. In 15 of these animals, an additional, relatively smaller artery was measured during prestimulation, after 5 min of stimulation, and following cessation of stimulation. These diameters ranged from 53–191 μm. The age distribution of the piglets used in nerve stimulation experiments was as follows: 1 day ($n = 4$), 2 days ($n = 3$), 3 days ($n = 3$), 4 days ($n = 4$), and 5–6 days ($n = 2$).

Effects of norepinephrine. In nine animals, 18 pial arteries were measured during a control injection of artificial CSF and 2–3 min after injection of norepinephrine [(−)Norepinephrine hydrochloride, Sigma] in artificial CSF under the window at the concentrations 2×10^{-6} M and 2×10^{-4} M. Responses were maximal and stable during this time interval. A large and relatively smaller artery were selected in each animal. The large arteries ranged from 90–303 μm and the paired, relatively smaller arteries ranged from 53–133 μm. The age distribution of the piglets used in exogenous norepinephrine experiments was 1–2 days ($n = 4$) and 3–5 days ($n = 5$).

Effects of arterial hypertension. In five animals, nine pial arteries were measured during normotension and during the first 1–2 min of sustained arterial hypertension. Arterial blood pressure was increased by intravenous infusion of dopamine (15 μg/kg) or prostaglandin-$F_{2\alpha}$ (25 μg/kg). We selected these agents for their capacity to increase arterial blood pressure. Due to the presence of the blood-brain barrier, it is unlikely that these agents were able to affect the pial circulation directly. Although dopamine is known as a vasodilator substance, at high concentrations, such as used here in piglets, it can increase arterial blood pressure by increasing peripheral resistance and cardiac output (10). The age distribution of piglets was 1 day ($n = 2$), 2 days ($n = 2$), or 5 days ($n = 1$).

Statistical Analysis. Pial arterial diameter and arterial pressure were analyzed using factorial design, repeated measures analysis of variance. If the F value was significant, then the Student-Newman-Keuls test was performed. The relationship between initial diameter or age and pial arterial response was determined by linear regression analysis. An α-level of $p < 0.05$ was considered significant in all statistical tests. Values are presented as mean ± SEM of raw values or as percentage change from prestimulation or control values.

RESULTS

Effects of sympathetic stimulation. Ipsilateral nerve stimulation reduced pial arterial diameter by 12 to 14% over the entire period of nerve stimulation (Fig. 1). Following cessation of nerve stimulation, diameters returned to prestimulation values. Arterial blood pressure did not change, compared to prestimulation, during the entire period of stimulation. Diameters of a second, relatively smaller artery from each animal ($n = 15$) decreased from 104 ± 9 μm during prestimulation to 88 ± 8 μm after 5 min of stimulation ($p < 0.05$) (change from prestimulation = 15%). Responses to nerve stimulation were independent of initial vascular size or age of the animals between 1 and 6 days (Fig. 2).

Effects of norepinephrine. Topical application of norepinephrine caused pial arteries to constrict from 149 ± 19 to 133 ± 18 μm at 2×10^{-6} M ($p < 0.05$) and from 159 ± 20 to 123 ± 16 μm at 2×10^{-4} M ($p < 0.05$) (18 arteries from nine piglets). The percentage change from control was greater at 2×10^{-4} M norepinephrine than at 2×10^{-6} M ($p < 0.05$) (Fig. 3). Constrictor responses were not dependent on initial vascular size. However, the constrictor response of pial arteries to exogenous norepinephrine was very weakly ($r = 0.44$), but significantly, correlated with age (Fig. 4).

Effects of arterial hypertension. An increase in arterial pressure from 68 ± 3 to 100 ± 6 mm Hg, produced by either dopamine or prostaglandin-$F_{2\alpha}$ infusion, resulted in pial arterial constriction from 154 ± 30 to 136 ± 26 μm ($p < 0.05$; nine arteries from five animals) (diameter decrease from normotension = 10%). Constrictor responses were independent of the initial size of the

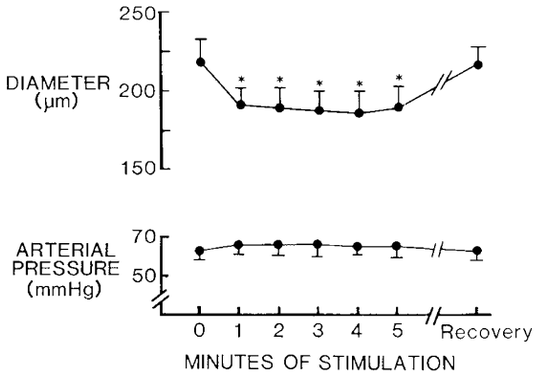

Fig. 1. Effects of sympathetic stimulation on pial arterial diameter in 16 piglets. Piglets of all ages were combined together. Values are mean ± SEM. *$p < 0.05$, compared to prestimulation or recovery. Arterial pH was 7.40 ± 0.02, P_{CO_2} was 35 ± 1 mm Hg, and P_{O_2} was >100 mm Hg.

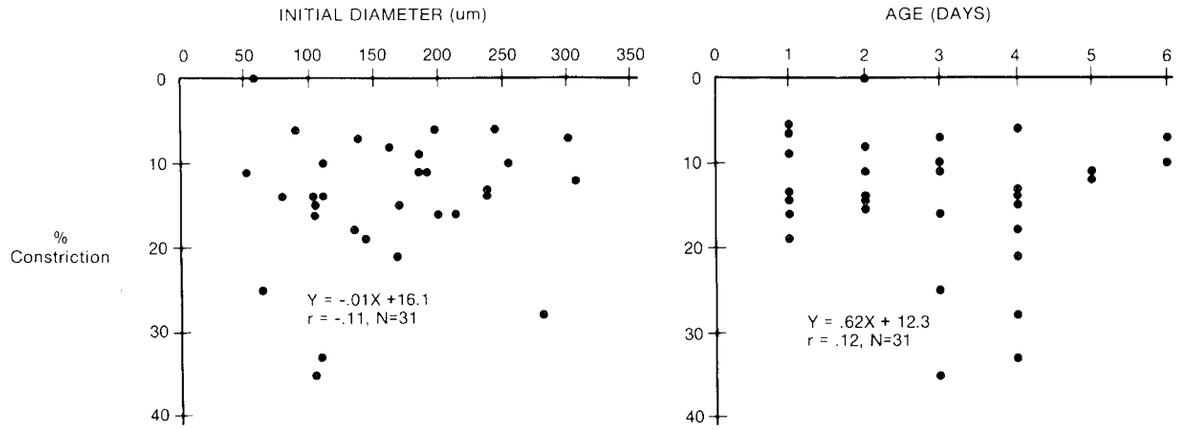

Fig. 2. Relationship between age or initial pial arterial diameter and response to sympathetic nerve stimulation in piglets. Sympathetic effects on pial arterial diameter were independent of both initial diameter and age.

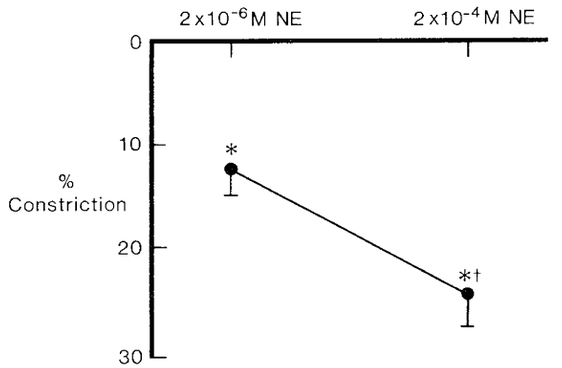

Fig. 3. Effects of norepinephrine on pial arterial diameter in nine piglets (18 vessels). Piglets of all ages were combined together. Values are mean ± SEM. *$p < 0.05$, compared to control; † compared to lower dose of norepinephrine. Arterial blood pressure was 62 ± 3 mm Hg during the first control, 63 ± 3 mm Hg during 2×10^{-6} M norepinephrine, 64 ± 3 during the second control, and 67 ± 4 mm Hg during 2×10^{-4} M norepinephrine. Arterial pH was 7.43 ± 0.03; P_{CO_2} was 34 ± 2 mm Hg, and P_{O_2} was >100 mm Hg.

artery (Fig. 5). Because of the small sample size, age effects were not examined.

DISCUSSION

The present study demonstrates that α-adrenergic mechanisms are operative in pial arteries of newborn pigs as early as 1 day of age. Sympathetic nerve stimulation reduced pial arterial diameter by up to 14–15%, and this response was maintained over the entire stimulation period. Exogenous norepinephrine also constricted pial arteries in a dose-dependent fashion. The results provide direct evidence that pial arteries are responsive to endogenous and exogenous norepinephrine in the immediate perinatal period in pigs.

The magnitude of pial arterial constriction due to sympathetic nerve stimulation in the piglet was 14–15%. In apparent contrast to other regional circulations, relatively large vessels such as pial arteries are important resistance vessels in the cerebral circulation (1). Constriction of this magnitude would have substantial effects on pial arterial resistance. Sympathetic effects on pial arteries were greater than the constrictor response resulting from a 50% increase in arterial pressure. The sympathetic effects in piglets are larger than the 6–7% constriction reported with the closed cranial window in adult cats (11, 12), a species in which nerve stimulation does not decrease CBF during normocapnia and normotension (11, 13). In the present study, the magnitude of the constrictor responses of pial arteries to exogenous norepinephrine was 12 and 24% for the concentrations 2×10^{-6} M and 2×10^{-4} M, respectively. These responses are comparable to that seen in adult cat pial arteries using the "open" cranial window (14) and adult mice (15), but greater than that found by Wei *et al.* (12) for the adult cat using the "closed" cranial window.

It has been reported previously that isolated cerebral arteries from pigs lack significant α-adrenergic receptors, and that the predominant response to exogenous norepinephrine is vasodilatation (16, 17). In addition, it has been found that activation of transmural nerves results in relaxation of isolated cerebral arteries from adult pigs (16, 17). In contrast, radioligand binding methods have provided evidence that α-adrenergic receptors, possibly of the α_2-subtype, are present in pial and parenchymal arteries from pigs (18, 19). In the present study, we have shown that sympathetic stimulation and exogenous norepinephrine constrict pial arteries of piglets. Similarly, in preliminary experiments, Wagerle *et al.* (20) found that sympathetic nerve stimulation reduces CBF in piglets. It is unclear which aspects of the studies lead to contradictory findings between *in vitro* and *in vivo* studies. One potential explanation is that α-adrenergic receptors are more important in younger than older pigs. This view is consistent with a finding by Hayashi *et al.* (7), who reported that cerebral arteries of fetal and newborn baboons constrict more strongly to exogenous norepinephrine than vessels from adult baboons. Another potential explanation is that extensive experimental manipulation of cerebral vessels in the *in vitro* preparations could have affected the α-adrenergic mechanisms in isolated vessels. For example, transmural electrical stimulation constricts isolated cerebral arteries of several species, but this response usually is not blocked by a variety of typical α-adrenergic antagonists (1, 21, 22). In contrast, sympathetic stimulation constricts pial arteries *in vivo* in cats and reduces CBF in rabbits and lambs, and these responses are blocked consistently by α-adrenergic antagonists (5, 14, 23). In addition, transmural electrical stimulation dilates cat and monkey cerebral arteries *in vitro* (24, 25), but sympathetic stimulation constricts cerebral arteries from these species *in vivo* (11–14). It has been difficult to demonstrate postjunctional α_2-adrenergic receptors in arteries *in vitro*, although these receptors mediate constriction in the same vascular bed *in vivo* (26). Adrenergic receptors in the pig cerebral circulation may be of α_2-subtype (19). However, at the present time, it is unclear which aspects of the studies mentioned above and the present study have led to contradictory findings concerning effects of sympathetic nerves and norepinephrine on pig cerebral arteries.

Previous studies in adult animals concerning the relationship between initial pial artery diameter and responsiveness to adrenergic stimuli have been controversial. Kuschinsky and Wahl (14) have found that sympathetic nerve stimulation and exoge-

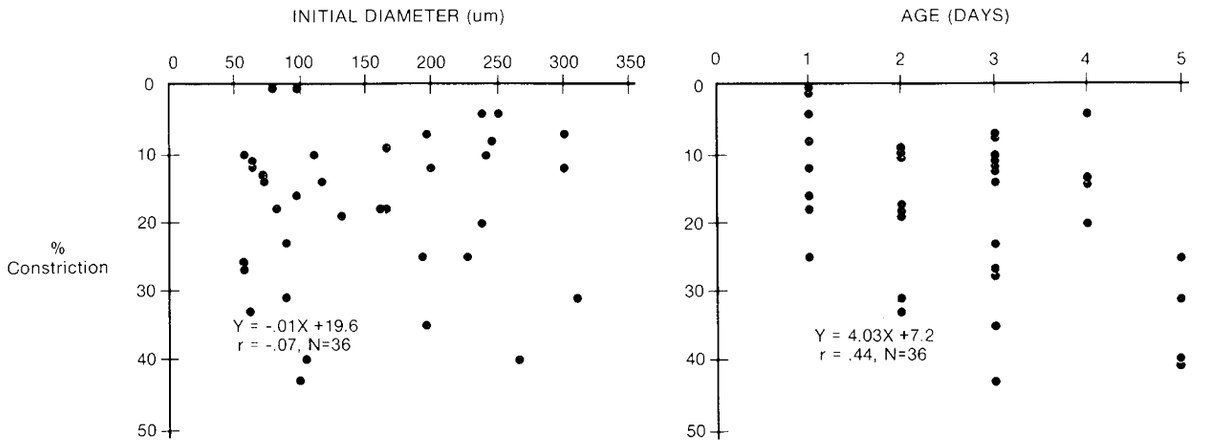

Fig. 4. Relationship between age or initial pial arterial diameter and response to exogenous norepinephrine in piglets. Effects of exogenous norepinephrine were independent of initial diameter but were mildly correlated with age ($p < 0.05$; $r^2 = 19$).

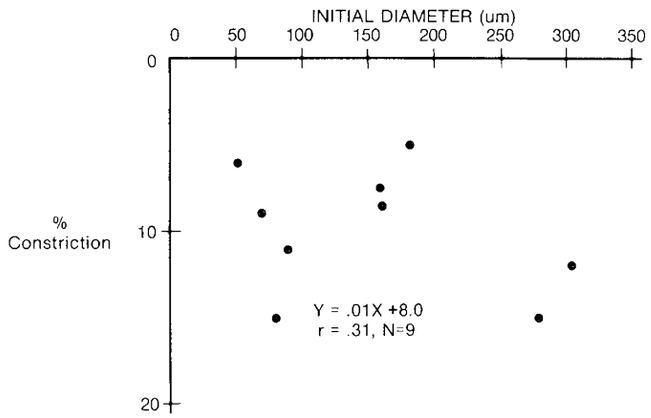

Fig. 5. Relationship between initial pial arterial diameter and response to arterial hypertension in piglets. During normotension, arterial blood pH = 7.35 ± 0.04, P_{CO_2} = 40 ± 6 mm Hg, and P_{O_2} > 100 mm Hg. During hypertension, arterial blood pH = 7.37 ± 0.07, P_{CO_2} = 38 ± 8 mm Hg, and P_{O_2} > 100 mm Hg.

nous norepinephrine constrict cat pial arteries which range from 40–240 μm in diameter. In contrast, Wei *et al.* (12) report that cat pial arteries greater than 100 μm in diameter constricted to both sympathetic nerve stimulation and exogenous norepinephrine, but smaller arteries were unresponsive to these stimuli. In our experiments, we found that the degree of responsiveness of pial arteries to sympathetic stimulation and exogenous norepinephrine was unrelated to initial vessel diameter. In additional experiments, we found that responses to another constrictor stimulus, arterial hypertension, also was unrelated to initial pial arterial diameter.

Sympathetic nerve stimulation has variable effects on cerebral vessels, depending on species studied and experimental conditions. In cats, sympathetic stimulation results in sustained constriction of pial arteries or reductions in CBF (12, 27). However, in primates, sympathetic stimulation initially reduces CBF by 25%, but blood flow to cortical gray matter, cerebral white matter, and caudate nucleus returns to control values by 1.5 to 5 min (27). In contrast, in rabbits, sympathetic stimulation reduces blood flow to cerebrum, cortical gray matter, and caudate nucleus, but only caudate blood flow returns to control levels during continued stimulation (27). In the present experiments, sympathetic stimulation resulted in a sustained constriction of pial arteries in newborn pigs. Thus, it appears that "escape" from sympathetic nerve stimulation is not a universal feature of the cerebral circulation.

Vascular responsiveness to sympathetic stimulation and exogenous norepinephrine in regional circulations may or may not develop simultaneously in newbon animals. In the renal circulation of newborn pigs, both nerve stimulation and exogenous norepinephrine increase renal vascular resistance (4). On the other hand, vascular responses to norepinephrine are inconsistent while sympathetic stimulation increases resistance in the femoral circulation in piglets (4). In the present study, we found that by 1 day of age in piglets, both sympathetic stimulation and exogenous norepinephrine constricted pial arteries.

The functional significance of cerebral sympathetic innervation in the newborn remains open to question. Hernandez *et al.* (6) reported that reflex activation of sympathetic nerves causes vasoconstriction in newborn puppies during asphyxia. On the other hand, even though electrical stimulation of sympathetic nerves decreased CBF during hypoxia, Wagerle *et al.* (5) found that reflex activation of sympathetic nerves does not affect cerebral vascular responses to hypoxia in lambs. The magnitude of the responses to sympathetic nerve stimulation in the present study indicates that this branch of the autonomic nervous system could participate in regulation of CBF in piglets. Previous studies have indicated that in adults, reflex activation of sympathetic nerves limits cerebrovascular dilation during hypercapnia (28), hypoxia (29), hemorrhagic hypotension (30), and limits increases in CBF during acute hypertension (1, 13, 31). Stressed newborns can suffer from one or more of these conditions, and we speculate that reflex activation of sympathetic nerves may contribute to the cerebrovascular reponses to these stimuli.

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