0031-3998/93/3403-0379$03.00/0
PEDIATRIC RESEARCH

Vol. 34, No. 3, 1993
Printed in U.S.A.

Possible Neuroprotective Properties of Flunarizine Infused after Asphyxia in Fetal Lambs Are Not Explained by Effects on Cerebral Blood Flow or Systemic Blood Pressure

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ABSTRACT. Neuroprotective properties of the calcium channel blocker flunarizine have been reported after hypoxic-ischemic insults in immature, infant, and adult rats. However, its effect on fetal regional cerebral blood flow (rCBF) and systemic blood pressure after severe asphyxia is not known. In 15 fetal lambs (3 to 5 d after surgery; gestational age at the experiment, 123.2 ± 2.5 d), arterial oxygen content was progressively reduced to 30% by restriction of uterine blood flow with an inflatable balloon occluder around the maternal common internal iliac artery. The rCBF was measured with radioactive microspheres at baseline condition, after 1 h of severe asphyxia, and at 30 and 120 min in the recovery phase. Immediately after the end of the occlusion period, fetuses randomly received either flunarizine or its solvent (0.5 mg/kg estimated fetal weight). No differences in rCBF changes between groups were observed during and after asphyxia. Changes in arterial blood pressure or fetal heart rate due to flunarizine could not be demonstrated either. Only five fetuses (33%) survived this degree of asphyxia longer than 24 h: four of the flunarizine-treated group and one of the control group. It is unlikely that this possible protective property of the drug is caused by its influence on rCBF, arterial blood pressure, or fetal heart rate in the phase immediately after asphyxia. (*Pediatr Res* 34: 379–384, 1993)

Abbreviations

rCBF, regional cerebral blood flow
FHR, fetal heart rate
Pa, arterial blood pressure
Pv, venous blood pressure
$[O_2]a$, arterial oxygen content
$Paco_2$, arterial carbon dioxide tension
post-1, postasphyxia 1; time = 90 min
post-2, postasphyxia 2; time = 180 min

Brain damage due to perinatal asphyxia is a clinically relevant target of research (1). In this respect, important results have been obtained in neonatal and in adult rats in which calcium channel blockers have shown structural and functional brain protective properties in various experimental setups. Newborn and infant rats, pretreated with the class IV calcium channel blocker flunarizine (2) and submitted to hypoxic-ischemic insults, had less brain damage compared with nontreated controls (3–5). Flunarizine treatment after induction of cortical damage in adult rats improved brain function and reduced infarct size (6). Regarding blood flow, flunarizine decreased the rate of the stimulated calcium influx into vascular smooth muscle cells of the rat tail and rabbit ear and, therefore, inhibited the peripheral vasoconstriction and vasospasm evoked by tissue anoxia (7). After 10 min of complete ischemia in the adult dog, the brain protective effect of nimodipine, a class II calcium channel blocker (2), was attributed to a nearly doubled cerebral blood flow (8).

The fetus reacts to hypoxia with an increase in cerebral blood flow to maintain cerebral oxygen delivery (9). The effect of flunarizine on fetal rCBF and on fetal cardiovascular parameters is not known. To mimic treatment after fetal pathophysiology, we chose to administer flunarizine after a period of severe asphyxia. The lack of oxygen results in energy failure, which leads to impeded ATP-dependent Na^+/K^+-transport. The ensuing decrease in membrane potential opens voltage-dependent calcium gates. Additionally, the decrease of the transmembrane sodium gradient diminishes outward calcium transport. Intracellular influx of calcium is an important factor in the mechanism of cell death (10). The intracellular calcium concentration is normally maintained near 0.1 μM, which is 10 000-fold less than the extracellular calcium concentration (11). Calcium shifts occurring with ischemic-anoxic energy failure are responsible for massive calcium overload in neurons, leading to activation of phospholipases. This results in accumulation of FFA and in swelling and edema of neurons. The latter further compromises oxygen supply (12).

Flunarizine, a possible neuroprotective drug, was studied in the chronic fetal sheep model, which allows accurate measurements of rCBF, FHR, Pa, and Pv during and after severe fetal asphyxia. The hypothesis tested was that flunarizine improves rCBF in the phase immediately after asphyxia and that this may lead to improved fetal outcome after severe asphyxia.

MATERIALS AND METHODS

Surgery. Surgery was performed in 15 pregnant Dutch Texel sheep. Gestational age varied between 115 and 124 d (mean ± SD = 119.2 ± 2.3 d, term = 147 d).

General anesthesia was induced with pentobarbital i.v. and maintained with 1% halothane in a 2:1 mixture of nitrous oxide and oxygen. Before surgery, the ewes received 1 g of ampicillin i.v. Instrumentation was performed as described previously (13).

Received December 6, 1991; accepted April 8, 1993.
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Briefly, a paramedian abdominal incision was made, and an inflatable balloon occluder was placed around the maternal common internal iliac artery. Catheters were inserted in the fetal axillary and femoral artery, and the tips were advanced to the level of the brachiocephalic trunk and descending aorta, respectively. In addition, fetal catheters were placed in the femoral vein, the tip was advanced into the inferior vena cava, and in the amniotic cavity. Electrodes were placed to record the fetal ECG and electrocorticogram, and a catheter in the fourth ventricle allowed sampling of cerebrospinal fluid. Catheters and wires were exteriorized to the ewe's flank.

Ewes were housed in individual cages, had free access to food and water, and were allowed to recover from surgery for at least 3 d before experiments were started. A continuous slow infusion (1 mL/h) of heparine in saline (10 U/mL) was used to maintain patency of fetal arterial and venous catheters. Guidelines for care and use of animals approved by the local Animal Medical Ethics Committee were followed.

Measurements. rCBF was measured by radioactive microspheres with a diameter of 15 μm. At random, one of four available microspheres (^{141}Ce, ^{103}Ru, ^{95}Nb, and ^{113}Sn) was injected. Aggregation was prevented by adding 0.05% Tween 80 to the medium. After homogenization in an ultrasonic 39°C water bath (Bransonic 5200, Soest, The Netherlands) for 20 min, approximately 0.5×10^6 microspheres were stirred on a vortex agitator and infused gradually over a period of 1 min into the inferior vena cava (14). Reference sampling (1.80 mL/min) was started from the brachiocephalic arch, 30 s before infusion, continued during infusion, and stopped 1 min after infusion, using a variable speed peristaltic pump (Harvard Apparatus 1210, Edenbridge, England).

Pa, Pv, and amniotic pressure were determined with the zero point at the level of the ewe's spine. These signals, together with the FHR derived from the pulsatile signal of the femoral artery, were led to a bioelectric amplifier (Hewlett-Packard 8800 series, Andover, MA), displayed on a monitor, recorded on an eight-channel strip chart recorder, stored on magnetic tape, and digitized and analyzed with a computer.

Immediately after microsphere injection, 2 mL of blood were withdrawn from the axillary artery and centrifuged (3 min at 13 000 rpm). Serum was frozen in liquid nitrogen and stored at −73°C to determine lactate concentrations. Blood gas values and pH from the fetal aortic arch were measured with an automated analyzer (AVL, Radiometer, Copenhagen, Denmark) and corrected for 39°C. Hb saturation was measured with an hemoximeter (OSM2 Hemoximeter, Radiometer). The $[O_2]a$ was calculated as follows:

$$[O_2]a\ (mM) = \text{Hb concentration (mmol/L)} \times \text{Hb oxygen saturation (\%/100)}$$

Experiments. Gestational age at the beginning of experiments varied between 119 and 129 d (mean ± SD = 123.2 ± 2.5 d). Baseline values were obtained during a control period of 2 h. Fetal acid-base state was analyzed every 15 min.

Figure 1 shows the experimental protocol. After measurement of rCBF in the baseline control period, severe asphyxia was induced by gradual reduction of maternal uterine blood flow by stepwise inflation of the balloon occluder around the common internal iliac artery. To maintain the fetus in a stable hemodynamic condition, uterine blood flow was gradually reduced over a period of 90 to 120 min until fetal $[O_2]a$ was reduced to approximately 30% of the baseline value. This latter asphyxic condition was maintained for 1 h. At the end of this period, at time = 60 min, rCBF was remeasured (asterisks in Fig. 1). Uterine blood flow obstruction was then discontinued by emptying the balloon occluder. At this moment the animals were randomized and treatment was started; seven fetuses received flunarizine (0.5 mg/kg estimated fetal weight), whereas the control group consisted of eight fetuses receiving the solvent, 10% 5-OH-propyl-β-cyclodextrine. To avoid possible side effects such as systemic hypotension and tachycardia, we administered flunarizine or the solvent in two dosages over a period of 1 h infused in the axillary artery. The first dosage was given immediately after the period of severe asphyxia, the second infusion started at time = 180 min. In the first animals, fetal serum levels of flunarizine were determined during various moments in the experiment. The rCBF was again determined at time = 90 min (post-1, which is during the first treatment) and at time = 180 min (post-2, just before the second treatment).

The experiment was ended when either the fetus had died or, in case of fetal survival, after 3 d. Then the ewe was killed by an overdose of pentobarbital, the fetus was removed and weighed, and correct catheter placement was confirmed. The fetal cerebrum was dissected into eight different anatomical entities: frontal cortex, parietal cortex, temporal cortex, striatum, hippocampus, cerebellum, thalamus, and medulla oblongata.

Calculations and data analysis. Different tissue samples were weighed (±1 g), put into test tubes, and preserved in fixative containing a 2% formaldehyde and 2.5% glutaraldehyde solution. All four isotopes were counted simultaneously. Radioactivity in the eight cerebral entities and in the reference samples was measured with an automatic gamma counter and sample changer system (analyzer model 45, Molsgaard Medical, Horsholm, Denmark). The rCBF was calculated with an ND680 programmable analyzer/computer system (Nuclear Data GmbH, Frankfurt, Germany).

FHR, Pa, and Pv, corrected for amniotic pressure, were averaged over 10-s periods using a computer program. Five of these epochs were averaged to calculate mean values. Data obtained at several moments in the experiment within one group were compared with a Friedman two-way analysis of variance, with time as the repeated measure. Differences between the flunarizine-treated group and the control group were tested with the two-tailed Mann-Whitney U test. A p value < 0.05 was taken to represent statistical significance.

RESULTS

Infusion of flunarizine resulted in fetal serum levels well within the therapeutic range, *i.e.* > 200 μg flunarizine/L serum (15).

Table 1 summarizes the fetal acid-base state at the four moments of blood flow measurement. $[O_2]a$ (mM), pH, P_{CO_2} (kPa), base excess (mM), and serum lactate concentration (mM) are expressed at baseline condition, at the end of the 1-h period of severe asphyxia (time = 60 min), at post-1, and at post-2 for both the flunarizine-treated group and the control group. Uterine blood flow restriction resulted in a reduction of the $[O_2]a$ to about 30% of baseline level. After 1 h of severe asphyxia, the mean pH had decreased to 7.08 and 7.09 in the flunarizine-treated group and the control group, respectively. In the recovery phase, the mean oxygen saturation did not return to baseline values. This resulted in an $[O_2]a$ significantly below baseline levels at post-1 and post-2, whereas pH and base excess increased only slightly. Serum lactate concentrations at post-1 and post-2 are in the same range as in the period of severe asphyxia.

Table 2 shows the weight-specific rCBF in mL/min × 100 g during baseline, asphyxia, and postasphyxia for eight cerebral areas. The amount of microspheres used was sufficient, as all of the dissected tissues and samples contained more than 400 microspheres (16). Adequate mixing was proven by the absence of significant differences between the amount of microspheres in left and right kidney. Baseline levels of blood flow in phylogenetic older structures as cerebellum, thalamus, and especially medulla oblongata were higher compared with younger structures as cortices (Mann-Whitney U test, $p < 0.05$). Blood flow to nearly all parts of the brain more than doubled in response to asphyxia. At post-1, during the first treatment, mean rCBF decreased compared with asphyxia but had not yet returned to baseline values. At post-2, rCBF in the flunarizine-treated group returned to baseline values, whereas rCBF in the control group remained

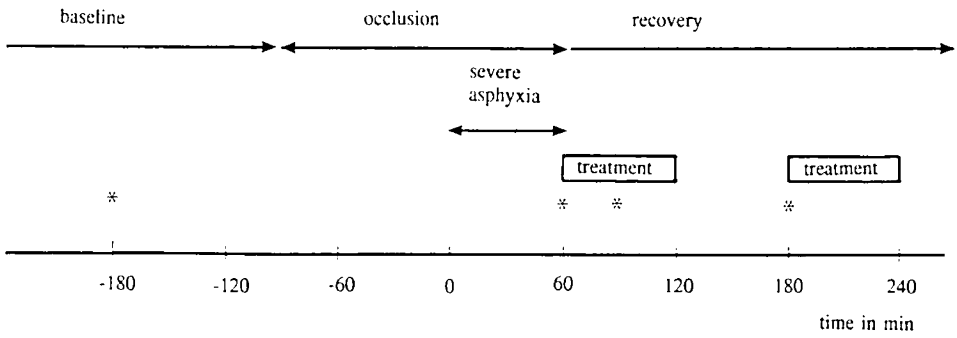

Fig. 1. Experimental protocol. *Asterisks* indicate rCBF measurement. The last two measurements correspond with post-1 and post-2 in the text. Treatment consisted of either flunarizine or its solvent.

Table 1. *Fetal acid-base state**

	Baseline	Asphyxia	Post-1	Post-2
Flunarizine group				
$[O_2]a$ (mM)	3.86 ± 0.44	1.13 ± 0.24†	2.64 ± 0.46†	2.48 ± 0.73†
pH	7.37 ± 0.02	7.08 ± 0.01†	7.13 ± 0.02†	7.27 ± 0.04†
P_{CO_2} (kPa)	4.79 ± 0.28	6.78 ± 0.49†	5.52 ± 0.26†	5.75 ± 0.41
Base excess (mM)	−3.5 ± 0.9	−15.4 ± 1.1†	−14.8 ± 1.4†	−9.7 ± 2.4†
Lactate (mM)	1.5 ± 0.3	11.2 ± 2.6†	9.4 ± 0.2†	10.8 ± 2.5†
Control group				
$[O_2]a$ (mM)	3.38 ± 0.34	1.14 ± 0.11†	1.86 ± 0.29†	1.56 ± 0.32†
pH	7.36 ± 0.03	7.09 ± 0.03†	7.12 ± 0.03†	7.15 ± 0.07†
P_{CO_2} (kPa)	4.61 ± 0.24	5.96 ± 0.45†	4.82 ± 0.23	5.71 ± 0.70
Base excess (mM)	−3.5 ± 1.0	−17.0 ± 0.7†	−16.8 ± 1.3†	−13.3 ± 2.6†
Lactate (mM)	1.8 ± 0.2	9.6 ± 0.8†	9.0 ± 0.4†	11.9 ± 2.5†

* Values are expressed as mean ± SEM. Asphyxia is at time = 60 min, post-1 is at time = 90 min, and post-2 is at time = 180 min. $n = 8$ for control group and $n = 7$ for flunarizine group, except at post-2 when $n = 7$ and $n = 6$, respectively.

† $p < 0.05$ (asphyxia, post-1, or post-2 *vs* baseline; Friedman two-way analysis of variance).

Table 2. *rCBF**

	Baseline	Asphyxia	Post-1	Post-2
Flunarizine group				
Frontal cortex	110 ± 32	225 ± 34†	184 ± 50	124 ± 20
Parietal cortex	117 ± 28	217 ± 43†	187 ± 62	121 ± 19
Temporal cortex	126 ± 39	203 ± 44†	165 ± 57	122 ± 23
Striatum	138 ± 32	265 ± 51†	190 ± 17	139 ± 21
Hippocampus	142 ± 42	247 ± 51†	161 ± 59	149 ± 23
Cerebellum	192 ± 71	350 ± 47†	293 ± 68	201 ± 33‡
Thalamus	210 ± 61	452 ± 80†	329 ± 85	229 ± 39
Medulla oblongata	265 ± 102	558 ± 76†	385 ± 123	292 ± 70
Control group				
Frontal cortex	114 ± 25	275 ± 50†	188 ± 34†	183 ± 18†
Parietal cortex	101 ± 20	260 ± 46†	179 ± 24†	164 ± 14†
Temporal cortex	89 ± 18	221 ± 41†	151 ± 27	152 ± 15†
Striatum	148 ± 30	341 ± 77†	223 ± 27	211 ± 29†
Hippocampus	120 ± 21	289 ± 65†	173 ± 37	200 ± 21†
Cerebellum	161 ± 32	422 ± 64†	325 ± 43	307 ± 22†‡
Thalamus	201 ± 29	501 ± 89†	320 ± 48	334 ± 23†
Medulla oblongata	196 ± 41	578 ± 92†	361 ± 53	377 ± 39

* Values are expressed as mean ± SEM (mL/min × 100 g). Asphyxia is at time = 60 min, post-1 is at time = 90 min, and post-2 is at time = 180 min. $n = 8$ for control group and $n = 7$ for flunarizine group, except at post-2 when $n = 7$ and $n = 6$, respectively.

† $p < 0.05$ (asphyxia, post-1, or post-2 *vs* baseline; Friedman two-way analysis of variance).

‡ $p < 0.05$ (flunarizine-treated group *vs* control group; two-tailed Mann-Whitney *U* test).

Table 3. *Fetal cardiovascular parameters**

	Baseline	Asphyxia	Post-1	Post-2
Flunarizine group				
FHR (beats/min)	172 ± 7	194 ± 22†	210 ± 13†	194 ± 17†
Pa (mm Hg)	46.2 ± 2.2	45.5 ± 3.7	44.7 ± 3.4	42.5 ± 4.3
Pv (mm Hg)	6.2 ± 1.6	5.5 ± 1.5	6.0 ± 1.6	5.9 ± 1.4
Pa-Pv (mm Hg)	45.0 ± 5.0	39.1 ± 3.9	41.0 ± 4.1	35.7 ± 4.8
Control group				
FHR (beats/min)	180 ± 12	221 ± 13†	212 ± 12†	206 ± 31†
Pa (mm Hg)	51.6 ± 2.5	48.2 ± 3.8	48.2 ± 3.7	47.3 ± 3.4
Pv (mm Hg)	4.5 ± 0.9	4.8 ± 3.8	7.5 ± 1.0	6.7 ± 1.1
Pa-Pv (mm Hg)	47.2 ± 3.4	43.5 ± 3.6	40.7 ± 3.4	42.3 ± 4.4

* Values are expressed as mean ± SEM. Asphyxia is at time = 60 min, post-1 is at time = 90 min, and post-2 is at time = 180 min. $n = 8$ for control group and $n = 7$ for the flunarizine group, except at post-2 when $n = 7$ and $n = 6$, respectively.

† $p < 0.05$ (asphyxia, post-1, or post-2 *vs* baseline; Friedman two-way analysis of variance).

significantly higher compared with baseline. However, no differences were demonstrated between both groups, except for cerebellar flow, which was higher in the control group at post-2.

Fetal cardiovascular parameters at the four moments of rCBF measurement are summarized in Table 3. During the experiment FHR increased, whereas Pa and Pv did not change. Perfusion pressure (Pa-Pv) in individual animals was calculated and did not change during the experiment. No differences between groups could be demonstrated.

In Figure 2 the time course of FHR, Pa, $[O_2]a$, and pH for both experimental groups is depicted. The time scale on the ordinate is the same as in Figure 1. No significant differences between the groups in any of the four parameters were demonstrated (two-tailed Mann-Whitney *U* test).

The entire experiment resulted in a mean fetal blood loss of 28.5 mL. This consisted of approximately 25 × 0.1 mL for the various determinations of the fetal acid-base state, added to 4 × 2.5 min × 1.80 mL/min for rCBF measurements, added to 4 × 2.0 mL for fetal serum analysis.

Fetal survival after severe asphyxia was poor: 10 animals (seven

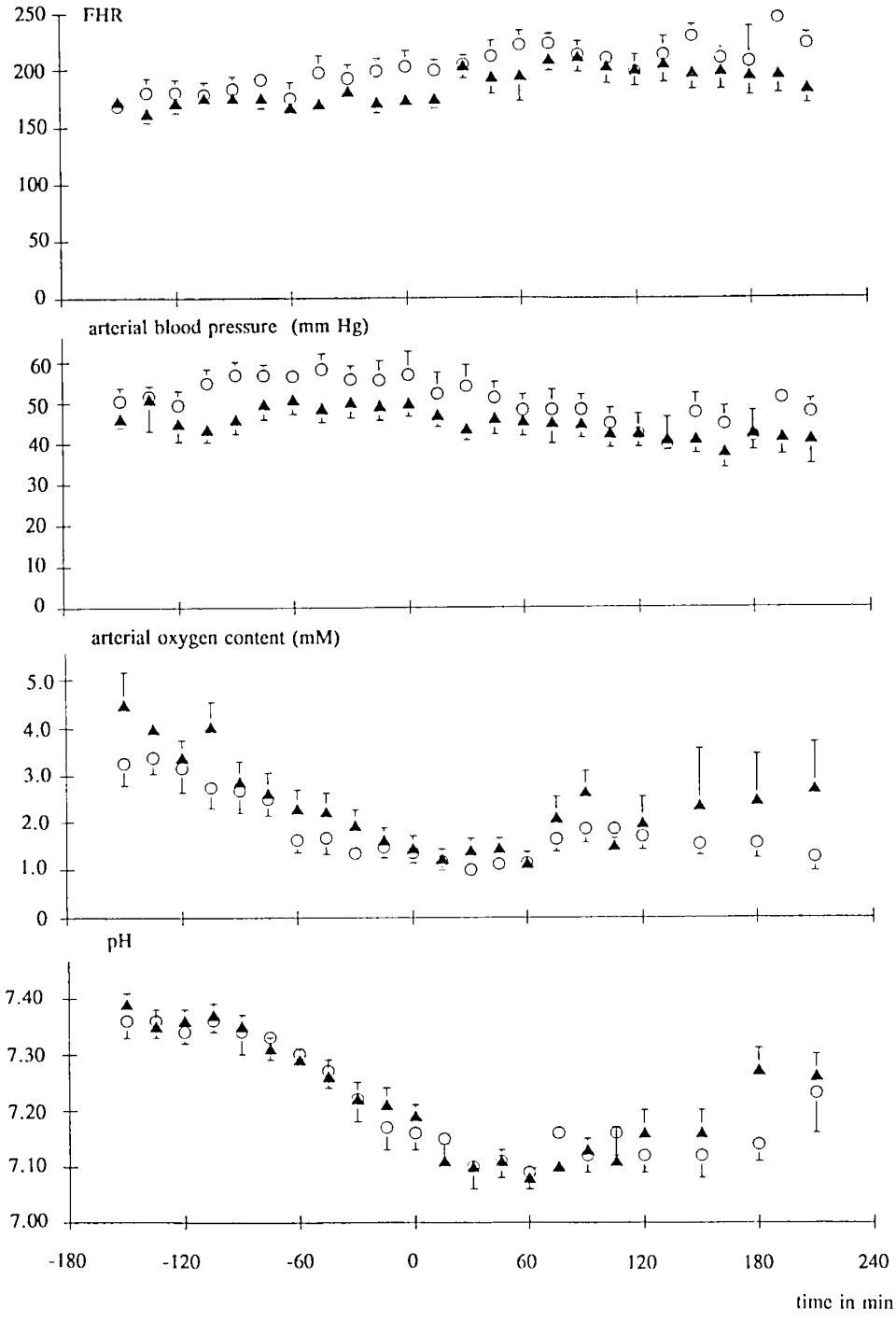

Fig. 2. Time course of FHR, Pa, $[O_2]a$, and pH (mean ± SEM). Time −180 to −120 min = baseline period; time −120 to 0 min = progressive reduction of uterine blood flow; time 0 to 60 min = 1 h period of severe asphyxia; time 60 to 240 min = recovery period. *Filled triangles* represent flunarizine-treated group; *open circles* represent control group.

of the control group *versus* three of the flunarizine-treated group) died during the first 24 h. In each group one animal survived a very short period, reducing the number of animals to $n = 7$ and $n = 6$ at post-2 for the control group and the flunarizine-treated group, respectively. In both groups one fetal lamb died between 1 and 3 d. The last three fetuses, all of the flunarizine-treated group, survived and were killed after 3 d.

DISCUSSION

To rationalize the use of calcium channel blockers in the treatment of brain ischemia-anoxia, two major theories are developed. The first theory is the augmentation of cerebral oxygen delivery. The mechanisms considered responsible are inhibition of calcium influx into vascular smooth muscle cells, thus relieving the vascular spasm originating from anoxia (7). Another mechanism involved is the inhibition of calcium influx into red blood cells, causing the erythrocyte deformability to remain intact (17). Studies on the impact of calcium channel blockers on rCBF and neurologic recovery after cerebral ischemia in adult dogs have yielded conflicting outcomes. Results varied from considerable benefits to total absence of improvement (8, 18, 19). The second theory is that calcium channel blockers would directly reduce calcium entry into neurons, thereby enhancing

resistance to injury. Flunarizine proved to be a potent blocker of low-threshold calcium channels (20). Maintaining low intracellular concentrations of calcium is an important modality in the prevention of cell death (10, 12). Van Reempts *et al.* (21) observed a reduced infarct size after photochemically induced thrombosis in spontaneously hypertensive rats and postulated on the basis of histologic findings that flunarizine might contribute to preservation of the integrity of endothelial cell membranes (reduction of platelet adhesion and vasogenic edema formation), of neuronal cell membranes (inhibition of calcium overload), and of glial cell membranes (prevention of cytotoxic edema formation). More recently, flunarizine enhanced neuronal survival in lumbar sensory ganglia from newborn rats after axotomy (22). The researchers suggested that this effect was caused by unknown intracellular acting mechanisms, distinct from blockade of voltage-dependent calcium channels.

Before considering the use of calcium channel blockers in the treatment of perinatal asphyxia, extensive animal research on the effects of these drugs on fetal brain circulation, metabolism, and function are needed (1). The present study not only focuses on the effect of flunarizine on the fetal rCBF after asphyxia but also analyzes the effect on FHR and fetal systemic blood pressure. Flunarizine is a highly lipophylic substance, easily crossing the blood-brain barrier. In humans it is used to treat neurologic disorders varying from migraine and vertigo to epilepsy (16). To mimic treatment in a clinical pathologic condition, we chose to start the infusion of flunarizine after a profound and prolonged period of asphyxia.

Oxygen delivery to the brain depends on both the $[O_2]a$ and the rCBF. The rCBF varies with gestational age. Baseline values in the present study correspond with those reported by others (23, 24). No differences in rCBF changes between both groups, either in the baseline period or asphyxia period or in the phase immediately after severe asphyxia during which flunarizine was administered, were observed. The $[O_2]a$ in both groups was comparable during baseline and asphyxia. Also, in the postasphyxic phase, the $[O_2]a$ between groups was not statistically different. It can only be speculated that the nonsignificant slightly higher $[O_2]a$ in the flunarizine-treated group might be caused by better brain functioning, improved myocardial performance, and placental perfusion, or by coincidence. At post-2, rCBF in the control group is still elevated compared with baseline, whereas rCBF has normalized in the flunarizine-treated group. Therefore, the net result of oxygen delivery is the same in both groups. The increased rCBF in animals suffering from hypoxia or asphyxia is in agreement with literature (9).

Reduction of maternal uterine blood flow with a balloon occluder around the common internal iliac artery resulted in severe asphyxia in all animals. An immediate effect of occlusion was a transient bradycardia with arterial hypertension. These cardiovascular parameters soon stabilized, resulting after 1 h of severe asphyxia in tachycardia and normal blood pressure in both groups. This is in agreement with data from others (24). The change from bradycardia to tachycardia and hypertension to normotension might be secondary to a sustained release of catecholamines (25), in combination with hypercapnia, which reduces vagal inhibition and thereby enhances sympathetic stimulation of the FHR (26). The degree and duration of asphyxia have their influence on cardiovascular reaction patterns (27, 28). One possible explanation for the final decompensation after severe asphyxia is hypoxic myocardial failure, which is accompanied by an elevation in central venous pressure and the development of hypotension (28). Cardiovascular reaction patterns were not influenced by the infusion of flunarizine, as can be seen from the FHR and Pa data in Figure 2. When asphyxia becomes too severe, oxygen delivery to vital organs can no longer be maintained (29). The ensuing anaerobic metabolism increases the amount of serum lactate in the fetus (28). In the present study, lactate concentrations increased to approximately 10 mM during asphyxia and remained at this level at least 2 h after the period of severe asphyxia. Although the $[O_2]a$ failed to recover to baseline values and the acid-base state did not normalize, fetal cardiovascular function in the first 3 h after asphyxia appeared to be adequate, as is suggested by a normal Pa and Pv. Perfusion pressure (Pa-Pv) also remained unaltered during the experiment in both groups.

The mean fetal blood loss of approximately 28.5 mL per animal in the present study did not result in a decrease in fetal Hb levels or even in fetal anemia. This is in accordance with the study of Brace and Cheung (30) who removed an average of 120.3 ± 5.1 mL of blood (30.8% of the initial blood volume) in a period of 2 h in fetal lambs. Complete restitution of fetal blood occurred in only 3 h, demonstrating that the dynamic fetal fluid system can accurately regulate its blood volume. Therefore, it is unlikely that the mortality, which was as high as 67% (10 of 15 animals) within the first day after the experiment, is caused by fetal hemorrhage resulting from the experimental protocol. The dead fetuses did not develop anemia before death. This strengthens the idea of ongoing pump failure during severe asphyxia, leading to insufficient placental perfusion, prolonged hypoxia, and progressive decompensation of both the metabolic and cardiovascular equilibrium. Most animals did not recover and died within 1 d. Of the five animals completely recovering from asphyxia and surviving longer than 1 d, four were treated with flunarizine. With these low numbers, only speculations can be made on protective properties of flunarizine. It also remains questionable to what extent fetal brain damage has contributed to the high percentage of early fetal demise.

In summary, the present data show that flunarizine, given after a period of severe asphyxia of 1 h in preterm fetal lambs, does not influence rCBF in the immediate postasphyxic period and does not affect FHR, Pa, or Pv. Mortality after such a long period of asphyxia is high; the effect of flunarizine on survival remains to be elucidated.

It is concluded that a possible beneficial effect of flunarizine on the fetal brain after asphyxia cannot be ascribed to an altered CBF, to its effect on systemic arterial or venous blood pressure, or to its influence on FHR.

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