Plasma Vasopressin, Renin, and Catecholamines during Nitroprusside-Induced Maternal and Fetal Hypotension in Sheep

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ABSTRACT. The release of vasopressin, renin, and catecholamines by the fetus during either maternal or fetal hypotension was examined in chronically catheterized fetal lambs. Nitroprusside was infused intravenously for 1 h into seven pregnant ewes (maternal hypotension) or nine fetal lambs (fetal hypotension); the rates were adjusted to achieve a 15 to 30% decrease in mean blood pressure. During maternal hypotension, mean $\pm$ SE vasopressin in maternal plasma increased from 1.2 ± 0.2 pg·ml⁻¹ to 208 ± 153 pg·ml⁻¹ and plasma renin activity increased from 1.5 ± 0.3 ng·ml⁻¹·h⁻¹ to 6.6 ± 1.6 ng·ml⁻¹·h⁻¹. Fetal vasopressin and plasma renin activity also increased during the same interval from 1.1 ± 0.3 to 16.9 ± 7.5 pg·ml⁻¹ and 3.7 ± 1.1 to 10.5 ± 2.85 ng·ml⁻¹·h⁻¹, respectively; but no changes were observed in fetal blood pressure, heart rate, or acid base status. During fetal hypotension, mean vasopressin in fetal plasma increased from 4.3 ± 3.4 pg·ml⁻¹ to 1054 ± 772 pg·ml⁻¹, plasma renin activity increased from 5.7 ± 2.2 ng·ml⁻¹ to 22.2 ± 7.1 ng·ml⁻¹·h⁻¹, and total catecholamines from 174 ± 58 pg·ml⁻¹ to 810 ± 416 pg·ml⁻¹. There was no change in fetal heart rate, acid base status, osmolality, or sodium concentration. The fetus became and remained hypertensive for at least 1 h after the end of infusion. This prolonged hypertension was associated with elevated levels of vasopressin and plasma renin activity. Peak vasopressin levels were proportional to the total nitroprusside dose in both the ewe and fetus (maternal $r = 0.796$, fetus $r = 0.870$). These experiments indicate that as in the adult, vasopressin and the renin-angiotensin system in the fetus are stimulated by euvoletic hypotension and may play an important role in the maintenance of fetal blood pressure during an hypotensive challenge. We speculate that the prolonged rebound hypertension represents immaturity of the fetus to fine tune the regulation, release, or metabolism of vasoactive mediators. More likely, the hypertension and elevated hormone levels represent homeostatic mechanisms to combat the nitroprusside-induced diminished cardiac output. Lastly, fetal release of vasopressin, renin-angiotensin, and norepinephrine during maternal hypotension suggests that they are sensitive indicators of early fetal compromise. (*Pediatr Res* 24: 73-78, 1988)

The fetus may be compromised by episodes of maternal hypotension (postural changes, regional anesthesia, placenta previa, etc.) or fetal hypotension (cord occlusion, fetal blood loss secondary to abruptio placentae, etc.) (1). In adults of several species, hypotension is known to stimulate several vasoactive systems which act to restore blood pressure towards normal values (2-8). The ability of the fetus to similarly withstand hypotension may have a significant influence on subsequent short-term and long-term outcome. The present studies were undertaken to determine the fetal response to both maternal and fetal hypotension with respect to fetal release of vasopressin, renin, and catecholamines in the maintenance of fetal blood pressure, heart rate, and arterial acid-base status.

MATERIALS AND METHODS

Surgery. Sixteen healthy mixed bred pregnant ewes, 2-4 yr old, and their fetuses, were catheterized at 110-125 days gestation. Surgery was performed under spinal anesthesia, supplemented with pentobarbital as described previously (9). The maternal femoral artery and vein were isolated and catheterized with no. 8 French feeding tubes (Argyle, St. Louis, MO) which were then advanced into the abdominal aorta. After abdominal incision and exposure of the uterus, the fetal neck was isolated and the carotid artery and jugular vein were catheterized with no. 5 French feeding tubes. The fetal skin, uterus, and maternal peritoneum were closed. Maternal fetal catheters were tunneled subcutaneously and brought out via a small stab wound in the maternal flank. At least 1 wk was allowed for recovery from the surgery before experimentation was begun. Surgery was performed at a mean gestational age of 128 ± 2.6 days.

Study. The animals were randomly divided into two experimental groups: group A, maternal hypotension (seven animals) and group B, fetal hypotension (nine animals). After a 30-min control period of stable blood pressure and heart rate measurements, freshly prepared sodium nitroprusside (Nipride, Hoffman LaRoche, Inc., Nutley, NJ) (0.33 mg·ml⁻¹ normal saline solution) was infused intravenously into the mother (group A) or the fetus (group B). The rate of infusion was adjusted to maintain a mean arterial blood pressure 15 to 30% below control levels in both groups. The range of total dose of nitroprusside administered was 7.8-140.2 mg for maternal hypotension and 1.34-18.26 mg (about 2.5 ± 1.75 mg·kg⁻¹) for fetal hypotension. The experimental period, which lasted 60 min, was followed by an additional hour of monitoring.

Arterial blood pressure was measured continuously using a Statham transducer (23 Db); by using amniotic fluid pressure as a reference corrections were made for extraneous factors (such as change in maternal posture) that might effect blood pressure

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measurement. Heart rate was determined by a cardiometer triggered by pulse pressure. Measurements were recorded on a multichannel Beckman polygraph. Arterial blood samples were taken before (0 min), during (30 and 60 min), and after (90 min) the nitroprusside infusion. The total amount of blood withdrawn per study was 20 ml from the mother and 16 ml (about 10 ml·kg⁻¹) from the fetus. Blood samples for assay of vasopressin and renin were collected in chilled EDTA tubes, catecholamine determination in chilled EGTA tubes, containing glutathione, and for blood gases, sodium, and osmolality determination in a heparinized syringe. Each sample was replaced with an equivalent amount of normal saline solution. The volume of blood withdrawn over the 2-h period of these experiments has been shown not to affect vasopressin levels (10).

Biochemical analysis. The plasma was separated at 4° C by centrifugation at 2000 × *g* 15 min and was stored at -30° C for later determination of plasma renin activity, catecholamines, vasopressin, electrolytes, and osmolality. Blood pH and gas tensions were measured immediately using microelectrodes and a Radiometer blood gas monitor.

Renin activity was measured by generation of angiotensin I using New England Nuclear Rianen angiotensin I [¹²⁵I] radioimmunoassay kit (New England Nuclear, Boston, MA), whose sensitivity is approximately 2 pg/sample with a precision of 0.55 ± 0.11 for values less than 2 ng·ml⁻¹·h⁻¹ and 7.40 ± 0.81 for values 7–10 ng·ml⁻¹·h⁻¹. Epinephrine and norepinephrine were measured by a radioenzymatic method, using Upjohn's Cat-A-Kit. Sensitivity of Upjohn's method ranges from 2–5 pg/50 µl for both epinephrine and norepinephrine. The average coefficient of variation within standard runs was 10% for epinephrine and 7.5% for norepinephrine. Vasopressin was analyzed by radioimmunoassay (11); the assay can detect 0.2 pg vasopressin/sample. Interassay variation was 17% and intraassay variation 8%.

Plasma sodium concentration and osmolality were measured using an Instrumentation Lab Flame Photometer and an Advanced Instrument Hi-Precision Research Osmometer. The coefficients of variation of the methods of determination of sodium concentration and osmolality were ±1 and ±2%, respectively.

Statistical analysis. All data are expressed as mean ± SE. Two animals in group A required increasing sodium nitroprusside infusion rates to maintain hypotension; they seemed to develop tachyphylaxis in response to the nitroprusside infusion. One of these experiments was stopped after 35 min to prevent possible cyanide toxicity, a side effect of nitroprusside. Because there was no statistical difference when the data from group A were analyzed with and without inclusion of this animal, the data presented include all seven studies; the 35-min sample data are included with the end of the experimental period data (60 min) for the other animals. All data were analyzed using a two-tailed paired *t* test. The vasoactive mediator data were transformed using a log function to decrease the influence of variance between the animals. All *p* values listed for vasopressin, renin activity, and catecholamines represent analysis using the log transformation. Not all measurements were made on all animals due to technical problems; however each mean represents measurements on no less than five samples.

RESULTS

Group A—maternal hypotension. Nitroprusside infusion into the ewe lowered mean blood pressure by 15–20% (12–20 mm Hg) to values significantly lower than control (*p* < 0.01) during the experimental period (Fig. 1). When the nitroprusside was discontinued blood pressure returned to preinfusion values within 2 min. Maternal heart rate remained statistically unchanged except at the beginning and immediately after cessation of the infusion, when it increased (*p* < 0.05). Fetal blood pressure and heart rate remained unchanged during and after infusion of nitroprusside into the mother. In only one animal was there a

Fig. 1. Changes in heart rate (top) and mean blood pressure (bottom) before, during, and after maternal nitroprusside-induced hypotension (as indicated). The solid line represents changes in the fetus and the broken line represents changes in the mother. Data expressed as mean ± SE. **p* < 0.05, ***p* < 0.01.

significant correlation between maternal and fetal blood pressures during the infusion. The vasoactive mediator response to maternal hypotension is displayed in Figure 2. Maternal vasopressin concentration increased from 1.2 ± 0.2 pg·ml⁻¹ to 208 ± 153 pg·ml⁻¹ (*p* < 0.0001) after 60 min of maternal hypotension. Peak maternal vasopressin levels significantly correlated with the total nitroprusside dose (*r* = 0.796, *p* < 0.05). Fetal vasopressin concentration also increased over the same interval from 1.1 ± 0.3 pg·ml⁻¹ to 16.9 ± 7.5 pg·ml⁻¹ (*p* < 0.004). Maternal plasma renin activity increased from a control value of 1.5 ± 0.3 to 6.6 ± 1.6 ng·ml⁻¹·h⁻¹ (*p* < 0.005). The rise in fetal plasma renin activity during the same period was from 3.7 ± 1.1 to 10.5 ± 4.3 ng·ml⁻¹·h⁻¹ (*p* < 0.05). Maternal total catecholamine concentrations increased from 251 ± 15 to 724 ± 179 pg·ml⁻¹ (*p* < 0.05) after 60 min of hypotension. Similarly, fetal total catecholamine levels increased during this same period from 351 ± 35 to 1206 pg·ml⁻¹ (*p* < 0.01).

The ewe that developed tachyphylaxis and required discontinuation of the nitroprusside after 35 min had an increase of vasopressin from 0.5 to 1120 pg·ml⁻¹; renin activity increased from 1.1 to 5.8 ng·ml⁻¹·h⁻¹, epinephrine from 91 to 454 and norepinephrine from 132 to 782 pg·ml⁻¹.

There were no statistically significant changes in the mean acid base status or blood gas tensions of the mother or fetus at any time interval (Table 1). The mean control plasma sodium concentration (maternal = 146 ± 1.2 mEq·l⁻¹ and fetal = 143 ± 2.0 mEq·l⁻¹) and osmolality (maternal = 300 ± 3.3 mosmol·kg⁻¹ and fetal = 297 ± 4.7 mosmol·kg⁻¹) were within normal range for sheep and remained unchanged throughout this experiment. The hematocrit also was unchanged (maternal: start = 29.9 ± 1.0%, end = 28.8 ± 1.4% and fetal: start = 34.2 ± 1.1%, end = 34.4 ± 1.1%).

Group B—fetal hypotension. Infusion of nitroprusside to the fetus significantly lowered mean blood pressure by 15–30% (Fig. 3) (*p* < 0.01). Within 2 to 5 min after discontinuation of the infusion, blood pressure rose above control value and the animals became significantly hypertensive (*p* < 0.05) for the remainder of the postinfusion observation period (1 h). The fetal heart rate remained unchanged during and after the infusion.

The vasoactive mediator response to fetal hypotension is displayed in Figure 4. Vasopressin concentration increased from

Fig. 2. Bar graph demonstrating changes in vasoactive mediators before, during, and after maternal hypotension: plasma renin activity (PRA, $\text{ng} \cdot \text{ml}^{-1} \cdot \text{h}^{-1}$) (hatched bar), vasopressin (VP, $\text{pg} \cdot \text{ml}^{-1}$) (open bar), catecholamines (CA, $\text{pg} \cdot \text{ml}^{-1}$) (composed of solid upper portion, epinephrine, and stippled lower portion, norepinephrine). The effects on the fetus, upper section of graph, and on the mother, lower section, are demonstrated. Data expressed as mean $\pm$ SE. * $p < 0.05$, ** $p < 0.01$.

Table 1. Blood composition (mean $\pm$ SE) before, during, and after nitroprusside infusion

	Maternal hypotension			Fetal hypotension		
	Control	Hypotension	Recovery	Control	Hypotension	Recovery
Fetal values						
pH	7.336 $\pm$ 0.013	7.323 $\pm$ 0.008	7.333 $\pm$ 0.012	7.391 $\pm$ 0.010	7.364 $\pm$ 0.014	7.371 $\pm$ 0.013
PO ₂ (torr)	25 $\pm$ 0.7	22 $\pm$ 1.3	25 $\pm$ 0.8	22 $\pm$ 0.9	23 $\pm$ 0.8	23 $\pm$ 0.8
PCO ₂ (torr)	46 $\pm$ 1.5	46 $\pm$ 1.8	45 $\pm$ 1.5	43 $\pm$ 1.1	44 $\pm$ 0.6	43 $\pm$ 0.8
Na (mEq $\cdot$ l ⁻¹)	143 $\pm$ 2.0	145 $\pm$ 2.2	144 $\pm$ 1.6	144 $\pm$ 1.4	143 $\pm$ 1.3	144 $\pm$ 1.0
Osmol (mosmol $\cdot$ kg ⁻¹)	297 $\pm$ 4.7	293 $\pm$ 2.5	302 $\pm$ 5.6	297 $\pm$ 2.3	300 $\pm$ 1.4	302 $\pm$ 2.5
Maternal values						
pH	7.444 $\pm$ 0.012	7.470 $\pm$ 0.018	7.434 $\pm$ 0.008			
PO ₂ (torr)	107 $\pm$ 2.0	103 $\pm$ 7.0	104 $\pm$ 2.6			
PCO ₂ (torr)	34 $\pm$ 1.1	31 $\pm$ 1.8	34 $\pm$ 1.0			
Na (mEq $\cdot$ l ⁻¹)	146 $\pm$ 1.2	146 $\pm$ 2.0	145 $\pm$ 2.0			
Osmol (mosmol $\cdot$ kg ⁻¹)	300 $\pm$ 3.3	300 $\pm$ 4.9	309 $\pm$ 5.6

Fig. 3. Changes in heart rate (*top*) and mean blood pressure (*bottom*) before, during, and after fetal nitroprusside-induced hypotension (as indicated). Data expressed as mean $\pm$ SE. * $p < 0.05$, ** $p < 0.01$.

4.3 ± 3.4 to 1054 ± 772 pg $\cdot$ ml $^{-1}$ after 60 min of hypotension ($p < 0.0002$). Peak vasopressin concentration correlated significantly with the total nitroprusside dose ($r = 0.87$, $p < 0.01$). Fetal plasma renin activity also increased from a control mean of 5.7 ± 2.2 to 22.2 ± 7.1 ng $\cdot$ ml $^{-1} \cdot$ h $^{-1}$ ($p < 0.004$) at 60 min. Significant changes were also found for epinephrine ($p < 0.04$) and total catecholamine ($p < 0.02$). Plasma levels of vasopressin and renin activity were still elevated 30 min after the end of infusion.

There were no statistically significant changes in mean acid-base state or blood gas tensions in either the ewe or the fetus after infusion of nitroprusside in group B (Table 1). The mean control plasma sodium concentration (145 ± 1.5 mEq $\cdot$ l $^{-1}$) and osmolality (297 ± 2.3 mosmol $\cdot$ kg $^{-1}$) were within normal range for sheep and remained unchanged during the experiment. The hematocrit also remained unchanged (start = $32.7 \pm 1.5\%$, end = $32.3 \pm 1.8\%$).

DISCUSSION

The present experiments show that both the pregnant ewe and the fetal lamb respond to induced hypotension by increased release into the circulation of vasopressin and renin and to a lesser extent norepinephrine. In the fetus, there was also a prolonged rebound hypertension associated with persistent high levels of vasopressin and plasma renin activity. In addition, fetuses of mothers with induced hypotension also respond early (30 min) with release of vasopressin followed by release of renin and norepinephrine by the end of the hypotensive period (60 min).

The degree of maternal or fetal hypotension produced in our experiment did not cause significant changes in fetal or maternal oxygenation, acid base, osmolal, or sodium composition. It is therefore unlikely that the activation of vasoactive systems were due to hypoxemia or hemoconcentration.

Release of vasopressin may be stimulated by hypotension or hypovolemia (2, 3, 12). In the present experiments hypotension was produced pharmacologically without directly altering blood volume; however, nitroprusside has been reported to produce intravascular volume depletion by sudden pooling of blood in dilated capacitance vessels (13). Therefore, it is possible that some of the hormonal responses we observed were secondary to hypovolemia as well as hypotension. The increase in and persistently elevated levels of plasma vasopressin that we observed in the fetus are similar to those observed by Ross *et al.* (14) except

Fig. 4. Bar graph demonstrating changes in vasoactive mediators before, during, and after fetal hypotension: plasma renin activity (PRA, ng $\cdot$ ml $^{-1} \cdot$ h $^{-1}$) (hatched bar), vasopressin (VP, pg $\cdot$ ml $^{-1}$) (open bar), catecholamines (CA, pg $\cdot$ ml $^{-1}$) (composed of solid upper portion, epinephrine, and stippled lower portion, norepinephrine). Data expressed as mean $\pm$ SE. * $p < 0.05$, ** $p < 0.01$.

that our peak levels of vasopressin and our nitroprusside infusion dose were higher. The difference in the protocol assay, or animal sensitivity and response to the nitroprusside infusion may be responsible for the varied findings. Inasmuch as there is a direct relationship between mean arterial blood pressure and levels of endogenous or exogenous vasopressin (15, 16), the vasopressin released by the mother or fetus during our experiments is most likely functioning as a vasopressor serving to support blood pressure. Perhaps vasopressin secretion is the cause of the tachyphylaxis to nitroprusside reported by others (17) and observed herein when two animals required a constantly increasing nitroprusside dose. Temporally, this increased dose requirement was associated with a marked increase in vasopressin concentration.

During a hypotensive stress to the fetal lamb or pregnant ewe, we observed significant increases in plasma renin activity. Pharmacologically induced hypotension also has been reported to stimulate renin and angiotensin release that act to support systemic blood pressure (5–8, 18) and uterine blood flow (19–23). Experiments on chronically cannulated fetal animals suggest strongly that a functional renin-angiotensin system is essential for normal fetal cardiovascular homeostasis (20, 24). Renin may be released during hypotension by direct neural mediation (5, 25) and/or by reflex feedback mechanism whereby angiotensin stimulates catecholamine release (26, 27). Furthermore, the duration of renin activity may be increased because nitroprusside diminishes mesenteric blood flow (28) and therefore, presumably decreases hepatic renin metabolism (29). Our results on plasma renin activity after induced hypotension suggest that the renin-

angiotensin system plays a significant role in both the pregnant ewe and fetal lamb to support the systemic and uterine circulations during pregnancy and fetal life.

The response of the sympathetic nervous system to hypotension is well described in adults. Broughton Pipkin *et al.* (20) report that this system is immature in the fetus and that other hormonal vasoactive systems are more important. The data presented herein suggest that despite this immaturity, the fetal sympathetic nervous system responds to hypotension.

When comparing maternal and fetal responses to nitroprusside-induced hypotension, in order to achieve the same percentage drop in blood pressure, the fetus required a higher dose of the drug than the pregnant ewe. Similarly, the fetus responded to the hypotensive stress with higher levels of all measured vasoactive mediators. These data might be interpreted as indicating a developmental change between the fetal and adult responses to an hypotensive stress. Because of the presence of vasoactive mediators, more nitroprusside is then needed to achieve the same degree of hypotension in the fetus compared with the pregnant ewe. Furthermore, when the hypotensive stress is removed in the fetus, there is a longer period of hypertension associated with elevated levels of vasoactive mediators. The results also may be explained by differences in the fetal and maternal vascular beds and their abilities to withstand hypotensive challenges.

Vasopressin, renin-angiotensin, and catecholamines show interactive effects with regard to secretion and homeostatic functions. Thus, despite greater responses seen with one vasoactive mediator over another, one cannot determine from our data what is the relative importance of each of the mediators in the defense of hypotension.

During maternal hypotension the stimulus for the rise in fetal vasopressin and plasma renin activity is likely to be uteroplacental hypoperfusion. High levels of vasopressin and components of the renin-angiotensin system would serve to maintain adequate fetal oxygen uptake (30). It is unlikely that the increase in vasopressin in fetal plasma is of maternal origin inasmuch as there is no evidence of its transfer across the sheep placenta (31). The rise in plasma renin activity in the mother and fetus during maternal hypotension may serve to maintain adequate placental blood flow either directly or indirectly by stimulation of prostaglandin E synthesis and by interaction with the sympathetic nervous system (21, 22, 32).

The nonpregnant (8) and pregnant ewe's blood pressure returned to preinfusion levels shortly after the end of nitroprusside infusion. The fetus became and remained hypertensive for more than 1 h after the end of the infusion. This prolonged hypertension was associated with elevated levels of vasopressin and renin activity. We speculate this represents immaturity of the fetus to fine tune the regulation, release, or metabolism of vasoactive mediators. Ross *et al.* (14) suggested that sustained elevated vasopressin levels were not due to decreased renal vasopressin clearance. Another possibility to account for persistently elevated levels of vasoactive mediators may be a consequence of the vasodilator properties of nitroprusside. By vasodilating the arterial and venous beds, sodium nitroprusside causes a decreased left ventricular filling pressure. Inasmuch as the fetal heart is already working at close to the maximum stroke volume, cardiac output might suffer if hormonal mediators are not secreted to help support the blood pressure. Thus, the elevation in levels of vasoactive mediators may represent the body's continued need to support the cardiac output.

Sodium nitroprusside has been used clinically only sporadically during pregnancy (33). Cyanide toxicity is a concern when using this drug. The dose we used (excluding the two maternal animals requiring large infusions) was within the suggested pharmacologically safe range to minimize the possibilities of cyanide poisoning in humans (34). Furthermore, none of the animals developed a metabolic acidosis, a sign of cyanide poisoning. Because the peak plasma level of vasopressin correlates with the total nitroprusside concentration, we speculate that there is an

interanimal variation in sensitivity to nitroprusside causing variable degrees of vascular vasodilation and variable falls in blood pressure that would then stimulate variable levels of vasopressin release to support the hypotension.

In summary, these experiments show that both the pregnant ewe and the fetus respond to induced hypotension by increased release of vasopressin, renin, and catecholamines. The correlation between peak vasopressin levels and total nitroprusside doses suggests that vasopressin is important in the maintenance of blood pressure in the fetus as well as the pregnant ewe and that the release of vasopressin may be proportional to the hypotensive challenge. However, the relative importance of the three systems studied remains to be examined. The release of vasopressin, renin-angiotensin, and norepinephrine by the fetus during maternal hypotension, despite a normal clinical status and normal arterial blood gas determinations, suggests that they are more sensitive indicators for fetal compromise than fetal heart rate or acid-base status. We speculate that the synergism between vasopressin and renin released by the pregnant ewe and the fetus during hypotension serve to maintain adequate uterine and placental blood flows. Finally, the persistent hypertension in the fetus after the end of nitroprusside infusion, may represent immaturity of the fetus' ability to precisely regulate, release, or metabolize vasoactive mediators.

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