Betamethasone-mediated vascular dysfunction and changes in hematological profile in the ovine fetus

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Laboratory for Pregnancy and Newborn Research, Department of Biomedical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, New York 14853; and Fetal Health Research Group, Department of Obstetrics and Gynecology, St. Thomas’ Hospital, London SE1 7EH, United Kingdom

Anwar, M. A., M. Schwab, L. Poston, and P. W. Nathanielsz. Betamethasone-mediated vascular dysfunction and changes in hematological profile in the ovine fetus. Am. J. Physiol. 276 (Heart Circ. Physiol. 45): H1137–H1143, 1999.—Glucocorticoid administration to fetal sheep induces a sustained systemic blood pressure rise and an associated increase in femoral vascular resistance. We utilized a small vessel myograph to compare isometric vascular responses of small femoral arterial branches from fetal sheep infused intravenously with either betamethasone or vehicle in vivo from 128 days gestation. Changes in hematological parameters were also determined. Betamethasone was infused for 48 h to produce fetal plasma betamethasone concentrations similar to those observed in human fetuses after maternal treatment with betamethasone to accelerate fetal lung maturation. When compared with vessels removed from vehicle-infused fetuses, vessels obtained from betamethasone-treated fetuses exhibited 1) enhanced sensitivity to depolarizing potassium solutions; 2) no differences in response to the thromboxane mimetic U-46619 or norepinephrine; and 3) differential responses to vasodilators, enhanced sensitivity to ACh, but decreased response to bradykinin and forskolin. In addition, erythrocyte and leukocyte counts were increased in betamethasone-infused fetuses. These observations indicate that multiple mechanisms operate to increase fetal vascular resistance during antenatal betamethasone exposure.

Betamethasone; antenatal; vascular resistance; blood pressure; blood cells

APPROXIMATELY 10% of all pregnancies are complicated by premature delivery, which remains the most important cause of perinatal morbidity and mortality (32). Survival rates of premature infants have increased dramatically (32) since the introduction of antenatal glucocorticoid therapy initiated after the classical studies by Liggins (28) demonstrating that prenatal maternal administration of synthetic glucocorticoids induced acceleration of fetal lung maturity. The benefits in improvement of neonatal respiratory function are undisputed; however, other wide-ranging and potentially harmful nonpulmonary effects of these steroids on fetal development are less well understood (13, 14, 25).

Glucocorticoids alter vascular function and produce hypertension in adult humans and animals (22, 38, 47). Several recent studies (13, 14, 43, 48) report an elevation of fetal blood pressure after infusion of glucocorticoids directly to the fetus. We have demonstrated that increased femoral vascular resistance is a factor in the elevation of fetal blood pressure during glucocorticoid exposure (13). Skeletal muscle vasculature plays an important role in control of peripheral vascular resistance and hence is a critical vascular bed to study. Prenatal glucocorticoid exposure in the rat results in persistent elevation of the blood pressure in adulthood, and offspring of pregnant rats treated with carbenoxolone, an inhibitor of the enzyme 11β-hydroxysteroid dehydrogenase, develop hypertension (29). 11β-Hydroxysteroid dehydrogenase converts cortisol to cortisone, thereby tending to protect the fetus from unwanted effects of cortisol in maternal plasma. All of these studies suggest that prenatal glucocorticoid exposure may lead to permanent and deleterious effects in the fetal vasculature.

To determine the mechanism of action of glucocorticoids on the fetal cardiovascular system, we examined the in vitro function of isolated peripheral small fetal femoral arterial branches in a small vessel myograph. Vessels were obtained from fetuses infused in vivo with betamethasone or vehicle. Tension responses to constrictor and dilator agonists were determined. In addition, because cortisol (48) and dexamethasone (22) reduce plasma volume in the sheep and rat, respectively, we investigated effects of betamethasone on erythrocyte and leukocyte numbers and plasma proteins.

METHODS

Care of Animals

Fifteen Rambouillet-Colombia crossed (Ovis aries) ewes bred on a single occasion and each carrying a single fetus (except one with a twin) of known gestational age were used for this study. All animals were housed in individual metabolism cages in sight of at least one other ewe. Lights went on at 0700 and off at 2100. All facilities were accredited by the American Association for the Accreditation of Laboratory Animal Care. Experimental procedures were approved by the Cornell University Institutional Animal Care and Use Committee and were in strict accordance with the American Physiological Society animal care guidelines.

Surgical Procedures and Infusion Protocol

Before surgery, food and water were withdrawn for 24 h. On the day of surgery, ewes were premedicated with ketamine (1 g) and glycopyrolate (1 mg) intramuscularly; anesthesia was induced with halothane (4%). Surgery was conducted under halothane general anesthesia at 123 days gestational age as previously described in detail (13). Briefly,
ewes were instrumented with polyvinyl catheters inserted in the maternal carotid artery and jugular vein, advanced into the arch of the aorta and superior vena cava, respectively. The fetal head was exteriorized through a midline laparotomy and hysterotomy. Fetuses were instrumented with polyvinyl catheters inserted via the carotid artery and jugular vein. An amniotic cavity catheter was also placed. Antibiotics were administered intraoperatively (ampicillin sodium, AMP-EQUINE; SmithKline Beecham, West Cheste, PA; 1 g iv to the mother and 0.5 g in the amniotic cavity). These doses were repeated two times daily for 5 days.

After vascular catheterization, fetal blood samples were drawn daily for analysis of blood gases and pH with a blood gas analyzer (ABL500; Radiometer, Copenhagen, Denmark; measurements were corrected to 39°C) to evaluate fetal condition. Food and water were available ad libitum. No studies were conducted for at least 5 days after surgery.

Beginning at 126 days gestational age, baseline in fetal blood pressure and heart rate were monitored by a pressure transducer (Cobe, Arvada, CO) connected to the fetal arterial catheter. After 2 days of baseline recording, either saline (n = 6, control group) or betamethasone (Celestone soluspan (beta-methasone sodium phosphate and betamethasone acetate suspension); Schering, Kenilworth, NJ; n = 9) was started at 1200 into the fetal jugular vein at a rate of 10 µg/h (13). A total dose of 0.48 mg was infused over the next 48 h. At the completion of the infusion period (130 days gestational age), ewes were euthanized with an overdose of pentobarbital sodium (Fatal-Plus; Vortech Pharmaceuticals, Dearborn, MI). Total plasma protein was estimated using a fibrometer (FibroSystem; BBL Product, Cockeysville, MD). Total plasma protein was estimated using a refractometer (Leica TS meter; Cambridge Instruments, Buffalo, NY).

Hematological variables. Blood samples were anticoagulated with disodium EDTA (1.5 mg/ml). Erythrocyte count, hematocrit, hemoglobin concentration, ratio of erythrocyte indexes (mean cellular volume and mean corpuscular hemoglobin concentration), and leukocyte (and differential) count were quantified in a Coulter counter (model S + IV; Coulter Electronics, Hialeah, FL).

Solutions and Reagents

PSS contained (in mM) 119 NaCl, 4.7 KCl, 2.5 CaCl2, 1.17 MgSO4, 25 NaHCO3, 1.18 KH2PO4, 0.027 EDTA, and 5.5 glucose at 37°C and was bubbled with 5% CO2 in 95% O2 to achieve a pH of 7.4. In KPSS, the sodium chloride was replaced with an equimolar concentration of potassium chloride. All PSS and KPSS reagents and NE, BK, ACh, and forskolin were acquired from Sigma Chemical (St. Louis, MO). U-46619 (9,11-dideoxy-9α,11α-methanoepoxy prostaglandin F2α) was supplied by Cayman Chemical (Ann Arbor, MI).

Data Analysis

Results are expressed throughout as means ± SE of all studies, and n is the number of fet al lambs. Tension is given as millinewtons per millimeter (mN/ mm) of artery length. Relaxation is expressed as percent relaxation of the tension after exposure to 5 mM NE. Cumulative concentration-response curves were constructed by fitting data to the logistic sigmoid function (log molar agonist concentration versus effect).

\[ E = E_{\text{min}} + (E_{\text{max}} - E_{\text{min}})/(1 - e^{KC_{50}}) \]

where E is the effect of the agonist, C is the molar concentration of the agonist, k is the slope of the curve, Emax represents the maximal tension induced by the agonist, and EC50 is the molar concentration of the agonist that produces a half-maximal response. Normality of distribution was tested by the Kolmogorov-Smirnov test. Significance was assessed by paired or unpaired Student’s t-test where appropriate or the nonparametric procedure of Mann-Whitney for data that were not normally distributed. Statistical significance was accepted at the level of P < 0.05.

RESULTS

Hemodynamic Variables

Mean arterial pressure, heart rate, diastolic blood pressure, and systolic blood pressure increased in response to betamethasone infusion. pH, blood gases, and base excess were not different between saline- and betamethasone-treated fetuses. Saline infusion did not alter any of the above variables (Table 1).

Vascular Reactivity

Artery diameter. The internal diameters of the femoral arterial branches studied were similar in control
saline and betamethasone-infused sheep (control: 374.5 ± 35.1 vs. betamethasone: 406.2 ± 43.31 µm).

Constrictor responses. The tension developed in response to KPSS was enhanced in the arteries from the betamethasone-infused fetuses (Fig. 1). The EC50 (control: 21.55 ± 0.03 vs. betamethasone: 21.46 ± 0.01, P < 0.05) was greater in betamethasone fetuses compared with the saline-infused controls, but the difference in the maximum responses (betamethasone: 5.78 ± 0.5 vs. control: 4.37 ± 0.5 mN/mm) only reached a significance value of P < 0.064. Because responses to KPSS were different between groups, correction of tension development to the agonists was not calculated as a percentage of the potassium contraction, as is commonly practiced.

Fetal femoral vessels showed concentration-dependent constriction to NE. There was no difference in sensitivity (EC50, betamethasone: -6.05 ± 0.11 vs. control: -6.24 ± 0.08) or maximum response (betamethasone: 6.42 ± 0.61 vs. control: 6.23 ± 0.54 mN/mm) to NE between saline-infused and betamethasone-infused fetuses (Fig. 2). Vessels from six of the seven betamethasone-treated animals studied had constrictor responses to U-46619. Vessels from four of six control animals tested responded to U-46619. The “responders” displayed a concentration-dependent constriction but no difference between saline- and betamethasone-infused animals (EC50, betamethasone: -6.38 ± 0.09 vs. control: -6.57 ± 0.09; maximum tension, betamethasone: 5.00 ± 0.36 vs. control: 5.39 ± 0.53 mN/mm, Fig. 3).

Relaxation responses. The tension developed to NE before forskolin addition was similar in vessels from saline-treated and betamethasone-treated animals (control: 6.15 ± 0.64 vs. betamethasone: 6.72 ± 0.48 mN/mm). Marked differences were observed in relaxation to forskolin, with the betamethasone group show-

### Table 1. Effects of intravenous infusion of betamethasone and saline for 48 h in ovine fetuses on fetal cardiovascular variables and blood gases

<table>
<thead>
<tr>
<th>Variable</th>
<th>Betamethasone Infusion</th>
<th>Saline Infusion</th>
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<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
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<tr>
<td>MAP, mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, Hz</td>
<td>166 ± 1.81</td>
<td>182 ± 4.34*</td>
</tr>
<tr>
<td>DP, mmHg</td>
<td>39 ± 3.25</td>
<td>60 ± 5.31*</td>
</tr>
<tr>
<td>SP, mmHg</td>
<td>53 ± 3.26</td>
<td>77 ± 5.93*</td>
</tr>
<tr>
<td>pH</td>
<td>7.35 ± 0.01</td>
<td>7.37 ± 0.01</td>
</tr>
<tr>
<td>Pco2, mmHg</td>
<td>50.1 ± 0.9</td>
<td>49.0 ± 2</td>
</tr>
<tr>
<td>Po2, mmHg</td>
<td>24.4 ± 1.0</td>
<td>23.2 ± 1.3</td>
</tr>
<tr>
<td>O2, %</td>
<td>63.8 ± 2.9</td>
<td>60.4 ± 3.3</td>
</tr>
<tr>
<td>Base excess, mmol/l</td>
<td>1.4 ± 0.6</td>
<td>2.5 ± 1.2</td>
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Values are displayed as means ± SE; n = 6 for both betamethasone and saline infusions. MAP, mean arterial pressure; DP, diastolic blood pressure; SP, systolic blood pressure. *Significantly different from preinfusion values at P < 0.05.
ing reduced relaxation to this agonist than the saline-treated controls (Fig. 4). The EC<sub>50</sub> for the betamethasone-treated fetuses was −7.73 ± 0.23. Although it is not possible to calculate the EC<sub>50</sub> for the controls, the percent relaxation at 10<sup>−9</sup> M was 52.

The tension developed to NE before the addition of the endothelium-dependent vasodilators ACh and BK was similar in saline-treated and betamethasone-treated animals (ACh protocols, control: 6.73 ± 0.60 vs. betamethasone: 6.66 ± 0.60 mN/mm; BK protocols, control: 6.35 ± 0.60 vs. betamethasone: 6.60 ± 0.48 mN/mm). Relaxation to BK was significantly (P < 0.05) diminished in betamethasone-treated fetuses (EC<sub>50</sub>, betamethasone: −8.75 ± 0.10 vs. control: −9.27 ± 0.12, Fig. 5). Maximum relaxation to BK was similar to controls (betamethasone: 98.5 ± 0.72 vs. control: 97.89 ± 1.28% relaxation of NE-induced tone). Sensitivity to the relaxant action of ACh was significantly (P < 0.05) enhanced in the betamethasone-treated group (EC<sub>50</sub>, betamethasone: −7.58 ± 0.12 vs. control: −7.20 ± 0.08, Fig. 6), but maximum relaxation was identical after exposure to ACh (betamethasone: 99.2 ± 0.54 vs. control: 99.97 ± 1.02%).

**Hematological Variables**

**Erythrocytes.** Forty-eight hours of betamethasone infusion was associated with a significant rise in fetal hematocrit, fetal erythrocyte count, and fetal hemoglobin concentration 48 h after infusion (Table 2).

**Leukocytes.** The total leukocyte count increased significantly in the betamethasone-treated animals, the result of a significant rise in the neutrophil count. In contrast, lymphocyte number fell significantly in response to betamethasone infusion (Table 2).

**Biochemical components.** Fetal total plasma proteins increased significantly in the betamethasone-treated group. The increase in fetal plasma fibrinogen concentration did not reach significance (Table 2). After betamethasone treatment, ACTH values decreased significantly from preinfusion levels, whereas the mean of cortisol values before and after infusion was not different (Table 2).

**DISCUSSION**

This study confirms our previous observation that betamethasone infusion directly to the ovine fetus at 0.85 gestation increases fetal mean arterial blood pressure. Investigation of the isolated small resistance branches of the femoral artery has demonstrated significant abnormalities of function, some of which could contribute to the increase in peripheral vascular resistance that accompanies the rise in fetal blood pressure.

**Fig. 4.** Cumulative concentration-response curves for relaxation due to forskolin on norepinephrine-induced tone in fetal ovine femoral arteries from betamethasone-infused (■, n = 7) and saline control (▲, n = 4) animals. Values are shown as means, and vertical lines indicate SE. *Significant difference between saline control and betamethasone-induced groups (P < 0.05).

**Fig. 5.** Cumulative concentration-response curves for relaxation due to bradykinin on norepinephrine-induced tone in fetal ovine femoral arteries from betamethasone-infused (■, n = 4) and saline control (▲, n = 5) animals. Values are shown as means, and vertical lines indicate SE.

**Fig. 6.** Cumulative concentration-response curves for relaxation produced by ACh on norepinephrine-induced tone in the fetal ovine femoral arteries from betamethasone-infused (■, n = 5) and saline control (▲, n = 5) animals. Values are shown as means, and vertical lines indicate SE.
that we observed on depolarization could result from an effect on voltage-gated calcium channels. Downregulation of sodium-calcium exchanger activity may also facilitate elevation of cell calcium by glucocorticoids (41).

Previous studies in the adult vasculature have suggested that responses to NE are enhanced by glucocorticoid treatment (47), but this was not observed in this study or in an earlier investigation (43) in which the fetal sheep were infused with increasing concentrations of NE before and subsequent to infusions of cortisol. Because the sensitivity to potassium was increased, greater sensitivity to NE might have been anticipated in fetal arteries exposed to betamethasone than in controls (1). The absence of altered sensitivity could indicate that NE-induced contraction is largely dependent on release of intracellular calcium rather than calcium influx. This conclusion is supported by Nakanishi et al. (31) who highlighted an important role for intracellular calcium release in fetal vascular smooth muscle of the rabbit.

Although this study has attempted to define the mechanisms contributing to glucocorticoid-induced hypertension in the fetal sheep, it has also shown that small arteries of the femoral circulation are responsive to NE, which agrees with one study of the femoral artery in vitro (17). Indeed, the pD2 was almost identical to that of the present study. These data contrast markedly to recent unpublished data from our laboratory in the femoral arteries of late-gestation fetal rats, which show no contraction to NE, but would agree with a marked constrictor response we have observed in the small arteries of the femoral circulation from the fetal baboon (3). The observation that some arteries responded to the thromboxane mimetic U-46619 and not others has also been described by Buzzard et al. (7) in immature rabbits (25% were nonresponders) and is unlikely to have been a methodological error introduced in the preparation of the arteries. This sensitivity to thromboxane is perhaps unsurprising, as the fetomaternal circulation is generally very sensitive to constrictor prostaglandins (8, 11), and levels of thromboxane B2, the stable metabolite of thromboxane A2, are high in the fetal sheep circulation (8).

The blunted response to the adenylate cyclase agonist forskolin suggested that betamethasone may increase vascular resistance by reducing intracellular cAMP. This conclusion is supported by a study of rat cultured vascular smooth muscle cells, which demonstrated a dexamethasone-induced reduction of adenylate cyclase activity and a decrease in cAMP (21). Because calcium is known to inhibit adenylate cyclase activity (2, 9, 10), it is possible that the glucocorticoid-induced increase in calcium influx may be the origin of reduced adenylate cyclase activity.

The reduced relaxation to BK observed in the glucocorticoid-treated fetal sheep could contribute to an elevation of vascular resistance, but paradoxically the enhanced sensitivity to ACh would tend to reduce resistance. The differential responses could arise from glucocorticoid effects on the BK or muscarinic receptors.

(13). It is important to study the in vivo response of the fetus to glucocorticoids, since fetal responses to glucocorticoids may differ qualitatively as well as quantitatively from those in the adult. For example, in the fetus, glucocorticoids increase plasma triiodothyronine concentration, whereas in the adult glucocorticoids depress triiodothyronine (44). The most profound in vitro abnormality in vascular function of the fetal small femoral vessels observed subsequent to in vivo betamethasone infusion was increased sensitivity to a depolarizing potassium solution, probably indicative of altered excitation-contraction coupling.

The alternative explanation is that glucocorticoids induce smooth muscle hypertrophy or hyperplasia. Because glucocorticoids are antimitotic, such a mechanism is unlikely. Constriction to depolarization is largely dependent on entry of calcium through voltage-gated calcium channels and subsequent activation of the contractile proteins. Pathways of contraction possibly affected by the glucocorticoids include ion channels, sensitivity of the contractile proteins, or mechanisms of calcium sequestration or release from intracellular stores. To our knowledge, no previous study has reported constrictor responses to potassium in fetal vessels, but one investigation in adult rabbits treated with high concentrations of dexamethasone has shown no difference in potassium-induced constriction compared with normal animals (40). It is relevant that other studies have shown increased calcium influx in cultured smooth muscle cells (18, 23) and in vascular smooth muscle in vivo (24) after treatment with dexamethasone. Hayashi et al. (18) suggested that this increase in calcium influx in the vascular smooth muscle cell line A7r5 occurs as a result of altered characteristics or increased number of dihydropyridine-sensitive calcium channels. The increased contraction

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<th>Table 2. Changes in hematological variables and plasma proteins as a consequence of betamethasone and saline infusion for 48 h in ovine fetuses</th>
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<tr>
<td><strong>Betamethasone Infusion</strong></td>
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<tr>
<td>Pre</td>
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<tr>
<td>Hematocrit, %</td>
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<tr>
<td>Erythrocyte count, 10⁶/µl</td>
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<tr>
<td>Hemoglobin, g/dl</td>
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<td>WCC, 10³/µl</td>
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<tr>
<td>Neutrophils, 10³/µl</td>
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<tr>
<td>Lymphocytes, 10³/µl</td>
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<tr>
<td>Total plasma proteins, g/l</td>
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<tr>
<td>Fibrinogen, g/l</td>
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<tr>
<td>Cortisol, ng/ml</td>
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<td>ACTH, pg/l</td>
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Values are displayed as means ± SE; n = 9 for betamethasone and n = 4 for saline infusions. WCC, total leukocyte count. *Significantly different from preinfusion values at P < 0.05.
or to preferential inhibition of prostacyclin synthesis (20, 26), which in some vascular beds makes a significant contribution to BK-induced relaxation, whereas ACh relaxation is predominantly nitric oxide (NO) mediated. Without the use of specific inhibitors of cyclooxygenase or nitric oxide synthase (NOS), we cannot confirm whether the role of prostacyclin is predominant in relaxation to BK in the arteries studied. Alternatively, as glucocorticoids have been shown to stimulate angiotensin-converting enzyme activity (15), the decreased sensitivity to BK could theoretically arise from increased metabolism of BK in the vessel. A recent study has indicated that, in the fetal coronary circulation (16), betamethasone releases NO and stimulates guanylate cyclase activity. Similarly, cortisol-induced renal vasodilatation in the adult sheep has been suggested to be a function of endogenous NO release (12). Glucocorticoid-induced NO synthesis could theoretically contribute to the enhanced relaxation to ACh observed.

The fetal arteries studied also had well-developed responses to the endothelium-dependent vasodilators, suggestive of high levels of activity of NOS and in agreement with recent studies in fetal sheep pulmonary arteries showing maximal NOS activity at term (33). Furthermore, in the renal glomeruli of the rat, dexamethasone potentiates the activity of soluble guanylate cyclase (27). Two recent reports have illustrated the presence of the inducible form of NOS (iNOS) in the rat (6) and the ovine fetal vasculature (37). The high level of NOS in the fetal vasculature could counteract the vasoconstrictor effects of glucocorticoid. In contrast, in certain situations, glucocorticoids reportedly inhibit iNOS (36). However, the current study clearly demonstrates that betamethasone amplifies ACh-sensitive relaxation in the femoral vasculature of fetal sheep at this stage of development. Further studies are required to dissect mechanisms that may account for differences between fetal and adult life.

The significantly higher postinfusion levels of total plasma protein, hemoglobin, hematocrit, and leukocyte count in the betamethasone-treated fetuses are indicative of a hemoconcentration effect of the steroid, which would increase viscosity and thereby lead to hypertension. Pries and co-authors (35) found that the resistance to flow in microvessels depends strongly on the hematocrit. Erythrocytes comprise a large proportion of the formed elements of blood, and as a consequence the hematocrit is the single most important factor in determining whole blood viscosity (4, 46). In the physiological range, log viscosity is positively correlated with hematocrit; and plasma viscosity is primarily determined by plasma protein concentration (4, 46). Therefore, the observed increased hematocrit and plasma protein values separately and together may be a contributory factor to the glucocorticoid-mediated hypertension.

Dexamethasone inhibits extravasation of leukocytes from the rat mesenteric postcapillary venules (42). In vivo glucocorticoid treatment results in the downregulation of L-selectin and CD18 expression on resting bovine neutrophils (5). These effects of glucocorticoids would explain the increase in the number of neutrophils in the vascular compartment. The dimensions of the capillaries are smaller than those of many cellular components of the blood. Blood cells must deform to circumnavigate the circulation. Leukocytes are 1,000-fold less deformable than the erythrocytes. Intravital microscopy demonstrates that leukocyte plugging is an important cause of intermittent flow in the microcirculation (39). In addition, because capillary lumens are not perfectly uniform, endothelial cell nuclei bulge into the intravascular space and may impede blood flow (34). As the proportion of neutrophils increases as observed in this study, the impact of leukocytes on the microvascular blood flow may contribute to the rise in blood pressure (19).

In conclusion, this study provides novel information regarding the responsiveness of isolated resistance arteries of the fetal sheep to constrictor and dilator stimuli and clearly demonstrates that glucocorticoids can induce enhanced in vitro responsiveness to depolarizing stimuli and reduced relaxation in response to physiologically relevant vasodilators together with a contribution of increased hematocrit and plasma viscosity. These observations provide the first clear indication of peripheral mechanisms that underlie the hypertensive response to fetal exposure to glucocorticoids.

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