Role of Vagosympathetic Fibers in the Control of Adrenocorticotropic Hormone, Vasopressin, and Renin Responses to Hemorrhage in Fetal Sheep

Charles E. Wood, Hong-Gen Chen, and M. Elizabeth Bell

Hemorrhage stimulates endocrine and cardiovascular reflex responses that are appropriate for returning blood volume and pressure to prehemorrhage levels. Fetal sheep respond to hemorrhage with increases in plasma adrenocorticotropic hormone (ACTH), cortisol, and vasopressin concentrations and plasma renin activity, but little is known about the afferent limb of the reflex(es) controlling these responses. Fetal sheep between 128 and 133 days' gestation were chronically prepared with vascular catheters. Five fetal sheep were subjected to bilateral section of the cervical vagosympathetic trunks; six fetal sheep were not vagotomized. Four to six days after surgery, the fetuses were subjected to withdrawal of 10 ml of blood every 10 minutes for 2 hours (130 ml total). Vagotomized fetal sheep responded to the hemorrhage with a greater decrease in central venous pressure than the intact fetuses and a slower restitution of fluid to the vascular space (estimated to be 17% of the hemorrhage volume in 2 hours) than the intact fetuses (estimated to be 28% of the hemorrhage volume in 2 hours). Both groups of fetuses, however, responded to the hemorrhage with increases in fetal plasma ACTH, cortisol, and vasopressin concentrations and plasma renin activity that were not significantly different. A posteriori analysis of the data by correlation analysis revealed that the fetal ACTH, vasopressin, and renin responses to the hemorrhage were more highly correlated to the changes in fetal arterial pH than to changes in fetal mean arterial pressure or central venous pressure. The results suggest the possibility that the fetal hormonal responses to hemorrhage may be secondary to the acidemia produced by reduced umbilical-placental perfusion during the period of hypovolemia.

(Circulation Research 1989;64;515-523)

In adult animals, hemorrhage stimulates secretion of adrenocorticotropic hormone (ACTH), corticosteroids, renin, and vasopressin via cardiopulmonary and arterial mechanoreceptors. Renin is controlled by mechanoreceptors in those areas and by the intrarenal baroreceptor and the macula densa. All three of these hormone systems also respond to hypoxia and/or hypercapnia, responses that may be at least partially mediated by the peripheral chemoreceptors. Results of experiments in adult animals suggest that atrial or other cardiac receptors with vago-sympathetic afferent fibers are of primary importance in the control of ACTH, vasopressin, and renin responses to small or moderate hemorrhage.

Fetal sheep respond to hemorrhage with increases in plasma ACTH, vasopressin, and renin concentrations. Presumably, receptor populations in the fetus controlling the secretion of these hormones are similar to those in the adult. One might predict that, in the fetus as in the adult, the hormonal responses to a nonhypotensive or mildly hypotensive hemorrhage would be attenuated by interruption of the vago-sympathetic afferent fibers from atrial or other cardiopulmonary receptors. This study was designed to investigate this possibility.

Materials and Methods

We studied 10 pregnant ewes of mixed Western and Florida native breeds. One sheep carried twins; the others carried single fetuses. On the day of study, the fetuses were between 128 and 133 days' gestation.
Surgical Preparation

We prepared the fetuses between 4 and 6 days before the first study. For 24 hours before surgery ewes were not fed but were allowed free access to drinking water. During surgery ewes were anesthetized with 1.0–2.5% halothane in oxygen. Using strictly aseptic techniques, we exposed the uterus with a midline incision. After incising the uterus, we delivered a fetal hind limb. We inserted a polyvinylchloride catheter (0.030 in. i.d., 0.050 in. o.d.) into the tibial artery and a larger catheter (0.040 in. i.d., 0.070 in. o.d.) into the saphenous vein. After catheterization of these two vessels, we sutured the fetal skin and returned the limb to the amniotic cavity. We delivered the second fetal hind limb and repeated the procedure. A polyvinylchloride catheter (0.050 in. i.d., 0.090 in. o.d.) with side-holes cut in the tip was sutured to the skin before returning the second hind limb to the amniotic cavity. The amniotic catheter was used for measuring amniotic fluid pressure during experiments. Before closing the incision in the uterus, 500 mg ampicillin (Polyflex, Veterinary Products, Bristol Laboratories, Syracuse, New York) was injected into the amniotic fluid. Catheters were filled with heparin (1,000 units/ml; Elkins-Sinn, Cherry Hill, New Jersey), plugged, and exited through a stab wound in the flank where they were protected by a cloth pouch sutured to the skin. In the case of twins, both fetuses were catheterized.

Six fetal sheep (including the twins) were prepared with vascular catheters only. Five fetal sheep were subjected to bilateral section of the cervical vagosympathetic trunks. After placing the vascular catheters, we located the fetal head and incised the uterus and the fetal skin over the trachea. We marsupialized the fetal skin to the wall of the uterus with clamps to prevent leakage of amniotic fluid; then we located and cut the vagosympathetic trunks. The fetal skin was sutured to the skin before returning the second hind limb to the amniotic cavity. The amniotic catheter was used for measuring amniotic fluid pressure during experiments. Before closing the incision in the uterus, 500 mg ampicillin (Polyflex, Veterinary Products, Bristol Laboratories, Syracuse, New York) was injected into the amniotic fluid. Catheters were filled with heparin (1,000 units/ml; Elkins-Sinn, Cherry Hill, New Jersey), plugged, and exited through a stab wound in the flank where they were protected by a cloth pouch sutured to the skin. In the case of twins, both fetuses were catheterized.

Analysis of Blood Samples

Plasma ACTH and cortisol concentrations were measured in all experiments (six intact and five vagotomized fetuses). Plasma ACTH concentration was measured by radioimmunoassay (RIA) in unextracted plasma using antiserum supplied by the

Experimental Protocol

All experiments were started between 0900 and 1100 hours to prevent possible variations between animals in resting hormone concentrations or magnitude of stimulated responses. Each fetus participated in one study. The order of experiments was randomized.

On the morning of an experiment the ewe to be studied was placed in a study cart and transported to the laboratory from the Health Center Animal Resources Department. From the time of transport to the time at which the first blood sample was drawn at least 1 hour elapsed to allow the ewe to accommodate to her new surroundings. During this time one fetal arterial catheter, one fetal venous catheter, and the amniotic fluid catheter were connected to Statham P23Db pressure transducers (Statham Instruments, Oxnard, California). Pressures were continuously monitored using a Beckman R611 (Fullerton, California) or Grass Model 7 (Quincy, Massachusetts) direct-writing recorder. The fetal heart rate was calculated from the phasic arterial pressure signal using appropriate Beckman or Grass cardiocodynameters. Fetal mean arterial pressure (MAP) was measured as the dumped output of a channel slaved from the phasic arterial pressure signal. Fetal mean arterial, central venous, and amniotic pressures and fetal heart rate were sampled and analog-to-digital conversions performed at 1-second intervals using a Keithley System 500 analog-to-digital converter. Fetal vascular pressures, heart rate, and amniotic pressure were not measured in one intact fetus because of a calibration error. Fetal central venous pressure (CVP) was not recorded in one vagotomized fetus because of a failure of the venous catheters.

Ten-milliliter blood samples were withdrawn from a fetal arterial catheter at 10-minute intervals for 120 minutes. At the beginning (0 minutes) and end (120 minutes) of each experiment, 10-ml blood samples were drawn from the maternal arterial catheter. This hemorrhage paradigm is similar to that used by Brace and Cheung.24 One maternal blood sample (5 ml) was drawn at the beginning of each experiment. Each blood sample was placed in a chilled plastic centrifuge tube containing 0.05 ml of 0.3 M Na2EDTA (Sigma Chemical Co, St. Louis, Missouri) per ml blood. All of these tubes were kept on ice until the end of the experiment when they were centrifuged at 3,000g for 20 minutes in a refrigerated (4°C) centrifuge. After centrifugation, the plasma was stored at −20°C until hormones were assayed. Additional blood samples (1 ml) were drawn anaerobically at 10-minute intervals from a fetal arterial catheter for analysis of fetal arterial pH, Po2, Pco2, and hematocrit. Fetal blood gases were measured in all experiments.

Analysis of Blood Samples

Plasma ACTH and cortisol concentrations were measured in all experiments (six intact and five vagotomized fetuses). Plasma ACTH concentration was measured by radioimmunoassay (RIA) in unextracted plasma using antiserum supplied by the
National Hormone and Pituitary Program.\textsuperscript{27} Plasma cortisol concentration was measured by RIA\textsuperscript{28} using antiserum no. 1460 (lot R2) from Radioassay Systems Laboratories (Carson, California) and [\textsuperscript{3}H]-[1,2,6,7]-cortisol from New England Nuclear Corp (Boston, Massachusetts) or Amersham Co (Arlington Heights, Illinois). Before assay, plasma was deproteinized with 50–100 vol of ethanol. Plasma renin activity (PRA) was measured in six intact and four vagotomized fetuses using a kit from Clinical Assays.\textsuperscript{29} For this assay, angiotensin I was generated in buffered (pH 5.7) plasma in vitro for one hour at 37° C. At the end of the incubation period the angiotensin I concentration was measured by RIA. Plasma vasopressin concentration was measured in five vagotomized and five intact fetuses by RIA using anti-vasopressin antiserum purchased from Amersham, [\textsuperscript{125}I]vasopressin from New England Nuclear, and synthetic arginine vasopressin from Sigma. Plasma assayed for vasopressin concentration was first deproteinized with acetone, as described by Cowley and coinvestigators.\textsuperscript{30}

Calculations and Statistical Analysis

All fetal intravascular pressures were calculated using amniotic fluid pressure as zero reference. Changes in the values of fetal hormonal and hemodynamic variables over time and between groups were assessed using two-way analysis of variance (ANOVA) corrected for repeated measures in one dimension, time.\textsuperscript{31} A posteriori comparison of individual means was performed using Duncan's multiple range test.\textsuperscript{31} Differences in maternal hormone concentrations in the two groups were tested using Student's \textit{t} test for independent groups. Correlations among variables were tested using standard correlations analysis. A significance level of $p \leq 0.05$ was used to reject the null hypothesis in all tests.

Changes in fetal blood volume were calculated from changes in fetal hematocrit as described by Brace.\textsuperscript{32}

Results

Initial fetal arterial blood pH values were 7.39±0.02 and 7.39±0.01; arterial blood PO$_2$ values were 22.3±1.4 and 24.0±1.5 mm Hg; and arterial blood PCO$_2$ values were 43.3±1.3 and 42.0±1.1 mm Hg in the intact and vagotomized groups (n=6 and 5), respectively. None of these values were significantly different between groups (tested by Duncan's multiple range test after two-way ANOVA for repeated measures in two dimensions).

Overall, hemorrhage decreased MAP (Figure 1, left; significant main effect of time in two-way ANOVA: $F=3.11$ with 120 and 960 df). There was no significant difference in the MAP response to hemorrhage in the two groups (no significant main effect of group or group×time interaction: $F=0.15$ and 0.90 with 1 and 8 and 120 and 960 df, respectively). Heart rate (Figure 1, right) was not significantly altered by the hemorrhage ($F=0.08$, 0.06, and 0.61 for main effects of group, time, and group×time interaction, with 1 and 8, 120 and 960, and 120 and 960 df, respectively). Vagotomy did alter the CVP response to the hemorrhage (Figure 2). Analysis of the CVP data by two-way ANOVA revealed a significant group×time interaction ($F=1.86$ with 120 and 840 df) but no significant main effects of group ($F=1.39$ with 1 and 7 df) or time ($F=0.91$ with 120 and 840 df).

Hemorrhage significantly decreased fetal arterial pH (Figure 3, bottom panel; significant main effect of time: $F=27.3$ with 12 and 108 df). The arterial pH decreased more rapidly in the vagotomized group (significant time×group interaction: $F=4.54$ with 12 and 108 df). In similar fashion, arterial blood PO$_2$ (Figure 3, middle) increased significantly (significant main effect of time: $F=14.75$ with 12 and 108 df), but more rapidly in the vagotomized group (significant time×group interaction: $F=2.02$ with 12 and 108 df). Arterial blood PO$_2$ (Figure 3, top) decreased in both groups equally (significant main effect of time: $F=2.42$ with 12 and 108 df).
Hematocrit (Figure 4) was significantly lower in the vagotomized fetal sheep at the beginning of hemorrhage (42±2% vs. 37±2% packed cell volume [PCV] in intact vs. vagotomized fetuses). The magnitude of the decrease in hematocrit during the course of the hemorrhage was greater in the intact fetuses (mean change, 6% PCV) than in the vagotomized fetuses (mean change, 4% PCV). Analysis of these data by ANOVA revealed significant main effect of time (F=54.6 with 12 and 108 df) and group×time interaction (F=3.54 with 12 and 108 df). Because the fetal sheep does not have a contractile spleen, acute changes in hematocrit have been used to calculate changes in blood volume.32 In the present experiments, the decrease in hematocrit during the hemorrhage may have been caused by transplacental and transcapillary refilling of the fetal vascular space. Red cells were diluted 14% in the intact group and 12% in the vagotomized fetuses, suggesting a more effective defense of blood volume in the intact group.

Initial fetal plasma ACTH concentrations were 41±8 and 60±7 pg/ml, and initial fetal plasma cortisol concentrations were 9.1±3.3 and 7.8±2.2 ng/ml in the intact and vagotomized fetuses, respectively (Figure 5). Initial values of ACTH and cortisol were not different in the two groups (Duncan's multiple range test). Hemorrhage stimulated similar ACTH and cortisol responses in the two groups (Duncan's multiple range test). Hemorrhage stimulated similar vasopressin and similar PRA responses in the two groups (significant main effect of time: F=4.08 with 12 and 84 df and F=37.2 with 12 and 96 df for vasopressin and PRA, respectively; insignificant main effect of group and group×time interaction for each hormone).

Correlations of fetal plasma ACTH and vasopressin concentrations and PRA to fetal MAP, CVP, and arterial pH were tested (Table 1). Logarithms of fetal hormone concentrations and activities were used in the correlations because logarithmic transformation linearized the relations (for example, see Wood et al33). In one intact fetus, plasma ACTH was significantly related to MAP and CVP, and PRA was related to MAP. In one other intact fetus, vasopressin was significantly related to MAP. In one vagotomized fetus, ACTH and vasopressin were signifi-
cantly related to both MAP and CVP, and in another vagotomized fetus, ACTH and PRA were significantly correlated to MAP (Table 1). Interestingly, in some of the experiments, ACTH, vasopressin, or PRA were correlated to increases in central venous pressure (e.g., fetuses Nos. 0071, Y70, and Y64). In contrast to the inconsistent or seemingly inappropriate (increasing hormone concentrations with increasing intravascular pressures) correlations between hormone concentrations and arterial or venous pressures, the hormone responses were much better correlated to the changes in arterial pH (Table 1). In 12 of 14 possible comparisons in intact fetuses and in 13 of 18 possible comparisons in vagotomized fetuses, correlations between hormone response and change in arterial pH were significant. The relations between mean values of fetal arterial pH and mean values of fetal plasma ACTH, vasopressin, and PRA are graphically summarized in Figure 7. The relation between ACTH or vasopressin concentration or PRA and arterial blood pH appeared to differ in the two groups (Figure 7). However, there was more variability in the slopes within groups than between groups. For this reason, there was no significant difference in the slopes between the two groups. Shown in Figure 8 are the distributions of correlation coefficients relating arterial pH, MAP, and CVP to the logarithm of plasma ACTH, vasopressin, and PRA.

Maternal plasma hormone concentrations were measured at the beginning of each experiment. Maternal plasma ACTH concentrations were 102±39 and 151±14 pg/ml, and plasma cortisol concentrations were 12.3±4.8 and 16.1±3.7 ng/ml in the groups with intact and vagotomized fetuses, respectively. Maternal plasma vasopressin concentrations were 2.5±0.1 and 2.9±0.3 pg/ml, and PRAs were 2.9±0.7 and 2.4±1.1 ng angiotensin I/ml/hr in the intact and vagotomy groups, respectively. There were no statistically significant differences in maternal plasma hormone levels in the two groups (tested by t test for independent groups).

Discussion

The results of this study suggest that the control of hormonal responses to hemorrhage in fetal sheep is...
### Table 1. Values of Correlation Coefficients Relating Fetal Plasma Hormone Concentrations to Arterial pH, Mean Arterial Pressure (MAP), and Central Venous Pressure (CVP).

<table>
<thead>
<tr>
<th></th>
<th>Log(ACTH) versus pH</th>
<th>Log(AVP) versus pH</th>
<th>Log(PRA) versus pH</th>
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<tr>
<td></td>
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<td>CVP</td>
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ACTH, adrenocorticotropic hormone; AVP, vasopressin; PRA, plasma renin activity.
a, No hemodynamics in this experiment; b, no AVP measurements in this experiment; c, no PRA measurements in this experiment; d, no central venous pressure in this experiment. *p<0.05.

different from that in the adult. Section of the cervical vagosympathetic trunks, which interrupts afferent fibers from atrial and ventricular mechanoreceptors, did not alter the magnitudes of the ACTH, vasopressin, or PRA responses to hemorrhage. In adult anesthetized dogs, acute vagotomy attenuated the vasopressin and adrenal corticosteroid responses to nonhypotensive or mildly hypotensive hemorrhage. ACTH and vasopressin are inhibited by afferent impulses from the atrial mechanoreceptors with afferent fibers in the vagus nerves and from carotid arterial mechanoreceptors. Renin is...
controlled by these receptors and by the intrarenal baroreceptor (reviewed by Davis and Freeman[13]).

The cardiopulmonary receptors are quite important in the mediation of the ACTH and vasopressin responses to slow or otherwise mild hemorrhage in adult animals. Renin responses to hemorrhage are less dependent on the activity of the cardiopulmonary receptors. Adrenal corticosteroid responses to 5 ml/kg hemorrhage in anesthetized dogs are attenuated by simultaneous inflation of a balloon in the right atrium.4 Blockade of cardiopulmonary receptors with intrapericardial injections of procaine blocked the vasopressin but not the renin response to hemorrhage of a volume of up to 35% of blood volume in conscious dogs.15 While afferent information from arterial mechanoreceptors may contribute to the ACTH, vasopressin, and renin responses to hypotensive hemorrhage, the cardiopulmonary receptors appear to be most important. Vasopressin and renin responses to progressive hemorrhage to 35% of blood volume in conscious rabbits were not attenuated by sinoaortic denervation.16 ACTH and corticosteroid responses to hemorrhage in sinoaortic denervated lambs were not smaller than responses in intact lambs.38 Chemoreceptors may influence the secretion of ACTH, vasopressin, and renin in adult animals during hypoxia and/or hypercapnia; however, chemoreceptor stimulation is unlikely to mediate the responses of these hormones to small or moderate hemorrhage because carotid sinus denervation (which would eliminate afferent fibers from carotid arterial chemoreceptors and baroreceptors) does not attenuate the ACTH, vasopressin, or renin responses to hemorrhage in postnatal lambs.38

Responses to hemorrhage in fetal animals differ from responses in adult animals in that moderate hemorrhage produces acidemia as well as alterations in arterial and/or venous pressures.39 The fetal acidemia is a respiratory acidemia caused by a primary increase in fetal Pco2. This condition, analogous to hypoventilation by the fetus, is most probably caused by decreased perfusion of the umbilical-placental circulation. Microsphere studies have demonstrated that hemorrhage reduces umbilical-placental perfusion.40

Fetal animals differ from adult animals in that MAP is regulated at a lower level. Chronic sinoaortic denervation in fetal sheep increased the variability of blood pressure and heart rate, indicating that fetal arterial baroreceptors are active at the regulated level of arterial pressure.41 However, the firing rates of the fetal arterial baroreceptors may be at or near the threshold for activation. If this were true, fetal arterial baroreceptors would be less responsive to decreases than increases in fetal arterial pressure. Fetal arterial Po2 is also regulated at a somewhat lower level than that in the adult. It is known that fetal peripheral chemoreceptors are active at this low Po2 and that the sensitivity of these receptors to changes in arterial oxygen tension resets after birth to adult levels.42 Little is known about the characteristics of atrial receptors in fetal animals.

Several studies have demonstrated that fetal sheep respond to hemorrhage with increases in plasma ACTH and cortisol,19 vasopressin,21 PRA, angiotensin II, and aldosterone.26 It is known that the secretion of these hormones is influenced by induced changes in arterial or venous pressure. For example, ACTH and vasopressin are stimulated by vena caval obstruction in fetal sheep, and the magnitudes of the responses are related to the severity of the obstruction,38 leading to the speculation that cardiovascular mechanoreceptors influence the secretion of these hormones. During hypovolemia in fetal sheep, plasma vasopressin and PRA responses correlated better to the volume of the hemorrhage than to the induced changes in MAP, leading to the speculation that volume receptors are important in the control of these two hormones.23 In one study, a significant correlation between plasma vasopressin and arterial blood pH during hypovolemia was noted.21 Other investigators have suggested that fetal hypoxia during hypovolemia may contribute to the vasopressin response.22 While several groups of investigators have studied hormonal responses to hemorrhage in the fetus, the populations of cardiovascular receptors responsible for mediation of these hormonal responses have received little attention.

As in studies by other investigators, the fetal hormonal responses to hemorrhage were not well correlated to the induced changes in arterial pressure.23,24 It is apparent from the results of the present study that fetal ACTH, vasopressin, and renin responses to mildly hypotensive hemorrhage in fetal sheep are more closely associated with the induced changes in arterial blood pH. The correlations with arterial and central venous blood pressure reveal mostly either nonsignificant relations or relations that are seemingly inappropriate for cardiovascular mechanoreceptor-hormone relations (increased hormone concentration with increased blood pressure). In contrast, the correlation coefficients calculated from relations between hormone concentration and arterial pH are high in most experiments. The association of hormone response to changes in pH would therefore suggest the possibility that the responses of these hormones to mild hemorrhage in the fetal sheep are mediated by the peripheral chemoreceptors rather than mechanoreceptors. It is also possible, however, that the hypercapnia produced by fetal hemorrhage stimulated the hormonal responses via medullary chemoreceptors. Raff and coworkers14 demonstrated that deafferentation of the carotid chemoreceptors attenuated the ACTH and corticosteroid response to isocapnic hypoxia but had no effect on the responses to hypercapnic hypoxia in anesthetized adult dogs.

While vagotomy did not alter the final magnitudes of the fetal ACTH, vasopressin, or PRA responses
to hemorrhage (Figures 5 and 6), it did alter the arterial PCO₂ and pH responses (Figure 3). The greater increases in PCO₂ and decreases in pH in the vagotomized group may reflect a greater decrease in fetal cardiac output and a concomitant greater decrease in fetal umbilical-placental flow in the vagotomized fetuses.

Vagotomy also altered the CVP response to the hemorrhage (Figure 2). Intact fetuses defended CVP well during this hemorrhage, while vagotomized fetuses responded to the hemorrhage with a substantial decrease in CVP. The maintenance of CVP in the intact fetuses may have been dependent on rapid restitution of blood volume. Because fetal sheep do not release red blood cells into the circulation after acute sympathetic stimulation, changes in hematocrit can be used to follow acute changes in blood volume. Assuming the fetal body weight was approximately 3.3 kg (calculated from the relation of gestational age to fetal body weight, as described by Robillard and Weitzman and assuming that fetal blood volume is 110 ml/kg), we can estimate that approximately 33 ml (28% of the volume removed between the 0- and 120-minute samples) of fluid reentered the fetal vascular space during the fetal hemorrhage. Using a similar approach, we can calculate that only 20 ml (17% of the volume removed) of fluid reentered the fetal vascular space in the vagotomized fetuses. This apparent difference in the rate of volume restitution may have been the cause of the greater decrease in CVP in the vagotomized fetuses. It is also possible that vascular compliance was lower in the vagotomized fetuses. In any event, the reduced rate of volume restitution and/or decreased vascular compliance may have contributed to an impairment of cardiac output and umbilical-placental blood flow, which, in turn, produced the greater increase in arterial blood PCO₂ and decrease in pH.

The difference in initial hematocrit in the intact and vagotomized groups may have also reflected alteration of fetal fluid balance by vagotomy. It is tempting to propose that the vagotomy produced an expanded plasma volume and, therefore, secondarily, a decrease in hematocrit by dilution of the red blood cells. This remains to be tested.

In summary, we have found that vagotomy altered the blood gas and CVP responses to slow hemorrhage in the sheep fetus but did not alter the magnitudes of the ACTH, vasopressin, or renin responses. The results suggest that the control of these hormonal responses to hemorrhage in the fetus are fundamentally different than in the adult. The data suggest the possibility that hormonal responses to hemorrhage in the fetus are stimulated by chemoreceptor activity, secondary to the acidemia or hypercapnia of fetal hemorrhage.

Acknowledgments

Synthetic human ACTH-(1,39) standard and anti-ACTH antiserum used in the ACTH radioimmunoassays were kindly provided by the National Institute of Diabetes and Digestive and Kidney Diseases and the National Hormone and Pituitary Program, University of Maryland School of Medicine. We would like to thank John Neal for photography and Kevin Fortin for typing.

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Key Words: vagus nerve • adrenocorticotropic hormone • vasopressin • renin • arterial pressure • central venous pressure • heart rate • hemorrhage • sheep
Role of vagosympathetic fibers in the control of adrenocorticotropic hormone, vasopressin, and renin responses to hemorrhage in fetal sheep.

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Circ Res. 1989;64:515-523
doi: 10.1161/01.RES.64.3.515

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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