Hemodynamic Responses of the Sheep Fetus to Vasopressin Infusion

HARRIET S. IWAMOTO, ABRAHAM M. RUDOLPH, LANNY C. KEIL, AND MICHAEL A. HEYMANN

SUMMARY The effects of intravenous infusion of vasopressin on the circulation of the fetus were studied in lambs in utero with chronically maintained intravascular catheters. Vasopressin infused in doses of 0.91-2.26 mU/min per kg fetal weight resulted in plasma levels of arginine vasopressin of 6.8-36.4 μU/ml; these levels are similar to those achieved during fetal hypoxia. Fetal mean arterial blood pressure increased from control levels of 47 ± 1.7 to 56 ± 1.9 mm Hg, and heart rate fell from 174 ± 4.1 to 144 ± 4.4 beats/min. Fetal cardiac output and its distribution and actual organ blood flows were measured before and during vasopressin infusion by the radionuclide-labeled microsphere technique. Combined ventricular output did not change significantly, but there was a redistribution of flow, with a marked reduction of the proportion of cardiac output to the gastrointestinal and peripheral circulations and an increase in the percent of cardiac output to the umbilical-placental, myocardial, and cerebral circulations. This redistribution was associated with a significant increase in fetal arterial Po₂ from 22 to 24 torr. Changes in heart rate, cardiac output, and distribution of cardiac output to various fetal organs are similar to those seen during fetal hypoxia and suggest that vasopressin release may play an important role in the fetal cardiovascular response to stress.

ARGININE VASOPRESSIN has been detected in the neurohypophysis (Alexander et al., 1974a; Skowsky and Fisher, 1977; Vizsolyi and Perks, 1976a, b) and plasma (Rurak, 1975; Skowsky et al., 1974) of fetal sheep by midgestation. It is not known, however, whether arginine vasopressin has a role in normal fetal physiology or in the fetal response to stressful stimuli. Plasma concentrations of arginine vasopressin in the sheep fetus have been shown to be elevated in response to various stimuli such as fetal hemorrhage, hypoxia, increased plasma sodium, and surgical manipulation (Alexander et al., 1974a, b; Rurak, 1975; Skowsky et al., 1973; Alexander et al., 1972).

The cardiovascular system of the fetus responds to neurohypophysial hormones; intravenous infusion of arginine vasopressin into the sheep fetus has been shown to cause an increase in blood pressure and a decrease in heart rate (Rurak, 1975; Alexander et al., 1976). At present there is no information regarding the specific actions of arginine vasopressin on the cardiovascular system of the fetus. It is known that, in the adult, arginine vasopressin causes bradycardia and vasoconstriction of certain vascular beds, resulting in an increase in blood pressure (Vizsolyi and Perks, 1976a; Altura and Altura, 1977; Schmid et al., 1974).

Our studies were undertaken to determine whether these responses are present in the fetus, and to characterize further the action of vasopressin on the hemodynamics of the sheep fetus. The radionuclide-labeled microsphere method (Rudolph and Heymann, 1967; Heymann et al., 1977) was used to determine the distribution of combined ventricular output to various vascular beds before and during an intravenous infusion of vasopressin. It was found that vasopressin caused an increase in fetal arterial blood pressure and bradycardia that was not fully reversed by atropine. Peripheral and gastrointestinal blood flows decreased, whereas blood flows to other parts of the body were not altered.

Methods

Studies were performed on 13 pregnant ewes of the Rambouillet breed with fetuses aged between 123 and 140 days of gestation; 12 ewes had single fetuses and one had twins. Nineteen studies were conducted on the 14 fetuses; five fetuses were studied twice on separate days.

The ewes were given epidural anesthesia with 2 ml of 1% tetracaine hydrochloride (Pontocaine HCl, Winthrop Lab) and placed in a supine position. Polyvinyl catheters were placed in the maternal dorsalis pedis artery and vein and passed centrally toward the inferior vena cava and aorta. The venous catheter was connected to an intravenous infusion of 5% dextrose in 0.9% saline for the administration of small amounts of sodium pentobarbital during surgery as needed. The arterial catheter was filled with heparin solution, 10 mg/ml, closed with a copper plug, and exteriorized on the maternal flank.

Through a ventral midline abdominal incision,
the pregnant horn of the uterus was exposed. A fetal hindlimb was exteriorized through a small uterine incision. Polyvinyl catheters (i.d. 0.030 inches, o.d. 0.048 inches) were placed in a pedal artery and vein and passed centrally to locate the tips in the descending aorta and inferior vena cava, respectively. The catheters were filled with heparin and sealed. Usually, arterial catheters were placed in both fetal hindlimbs. A second small incision was made in the uterus over the neck of the fetus, and catheters were placed in a carotid artery and jugular vein. A catheter also was placed into the amniotic cavity. Kanamycin sulfate (800 mg) and penicillin G (1 million U) were administered on the day of surgery and each day thereafter.

In three fetuses we placed an electromagnetic flow transducer around the common segment of the umbilical arteries, as described previously (Berman et al., 1975). Briefly, an incision was made in the uterine horn near the posterior portion of the fetus. The descending aorta was approached retroperitoneally from the left flank, and the cuff-type calibrated flow transducer (i.d. 4-5.5 mm; C and C Instruments) was placed around the isolated descending abdominal aorta distal to the origin of the iliac arteries (common umbilical artery). This instrument measured umbilical-placental blood flow as well as a minor contribution of flow destined for the sacrum, pelvis, and urinary bladder (Berman et al., 1975). The purpose of implanting the flow transducers was to monitor umbilical blood flow continuously and to examine the sequential changes in umbilical blood flow during vasopressin infusion.

When all surgical procedures were completed, the catheters were tunnelled subcutaneously to the ewe’s flank where they were protected by a cloth pouch sewn to the skin. The ewe’s abdomen was then sutured in layers.

We performed studies on the fetuses after at least 2 days of recovery while the ewe stood quietly in a stall. Fetal, maternal, and amniotic catheters were fitted to sterile three-way stopcocks and connected to Statham P23Db pressure transducers positioned at the ewe’s midabdomen. Pressures and fetal heart rate were recorded on a Beckman eight-channel Dynograph direct writing recorder. The fetal pressures were corrected for amniotic fluid pressure at the end of the experiment.

Control fetal and maternal arterial blood samples were obtained for the determination of plasma arginine vasopressin, plasma osmolality, blood gases, pH, and hematocrit. Five fetuses received an intravenous infusion of vehicle alone (5% dextrose in water) during the control period. In eight of 19 studies, fetal cardiac output and blood flow distribution were determined by the nuclide-labeled microsphere method by injecting 15-µm nuclide-labeled microspheres into the inferior and superior venae cavae of the fetus while reference samples were withdrawn from the descending aorta and carotid artery.

We infused Pitressin (Parke-Davis and Co.) or synthetic arginine vasopressin (Bachem, Inc.) in 5% dextrose in water, using a Harvard pump. Twelve sheep in 16 studies received Pitressin, and two sheep in three studies received synthetic arginine vasopressin. The hormone was infused at a flow rate of 0.1-0.2 ml/min in amounts of 1.6 mU/min per kg based on fetal weight estimated by gestational age. The actual fetal weight was measured at the end of the experiment in eight studies, and the actual rate of vasopressin infusion ranged from 0.91 to 2.26 mU/min per kg, with a mean rate of infusion of 1.37 ± 0.11 mU/min per kg (mean ± SEM). After 30 minutes, when it was evident that the fetal blood pressure and heart rate responses had been stable for at least 15 minutes, a second set of blood samples was drawn. Microspheres were again injected for determination of blood flow distribution during vasopressin infusion. In seven studies, pressures were monitored and blood samples were obtained for up to 2 hours after the infusion had been stopped.

At the end of the studies, the ewe was anesthetized with an intravenous injection of sodium pentobarbital and killed. The eight fetuses that received microspheres were removed from the uterus and dissected as described previously (Rudolph and Heymann, 1967; Heymann et al., 1977). The individual organs were incinerated in an oven and counted for radioactivity in a 512-channel multichannel pulse height analyzer (Searle Analytic). Fetal blood flow to the various organ vascular beds was calculated with the aid of a 370 IBM computer. Flows were calculated from the known counts in the particular organ, counts in the reference sample, and the withdrawal rate of the reference sample (Heymann et al., 1977). As a check on adequate mixing of the microspheres, right and left kidneys and hemissections of the brain were counted separately.

Plasma samples for arginine vasopressin determination were extracted with Bentonite and assayed by radioimmunoassay (Skowsky et al., 1974). Antibodies to vasopressin were produced in New Zealand White rabbits by repeated injections of Freund’s complete adjuvant and synthetic arginine vasopressin (Schwarz/Mann, 262 U/mg) coupled to bovine serum albumin. Each extract was reconstituted to 0.5 ml with 0.05 m phosphate buffer containing bovine serum albumin, 1.25 mg/ml, and duplicate 0.2-ml samples were assayed. Synthetic arginine vasopressin (357 U/mg) obtained from Ferrin Pharmaceuticals Ltd. was used for standards and iodination. The values reported were not corrected for the hormone lost during extraction. The antibody cross-reactivity with oxytocin and vasotocin was less than 0.01%. The mean recovery for arginine vasopressin was 65-98%. Other details concerning the assay are published elsewhere (Keil and Severs, 1977).

Plasma osmolality (accuracy ± 1 mOsmol/kg H₂O) was determined on an Advanced Osmometer.
(model 3W, Advanced Instruments, Inc.). Blood gases and pH were determined on a Radiometer blood gas analyzer (HM73, London Co.). Blood flow distribution, blood gas, pH, hematocrit, and plasma arginine vasopressin concentration data before and during vasopressin infusion were compared by paired t-test. Fetal heart rate and blood pressure were analyzed by one-way analysis of variance and the Newman-Keuls test.

Results
The five fetuses that received 5% dextrose alone during the control period showed no changes in plasma arginine vasopressin levels, blood gases, pH, or osmolality as a result of the infusion.

Arginine Vasopressin Concentrations (Table 1)
Mean fetal plasma concentrations in the control period were 4.83 ± 1.17 pg/ml (1.73 ± 0.40 μU/ml, mean ± SEM) and were not significantly different from the maternal concentrations of 3.16 ± 0.70 pg/ml (1.13 ± 0.25 μU/ml). One fetus (9A) had an unexplained, high control concentration of arginine vasopressin, 24.5 pg/ml (8.74 μU/ml).

Intravenous infusion of either Pitressin or synthetic arginine vasopressin into the fetus significantly elevated fetal plasma arginine vasopressin concentrations to 64.2 ± 5.7 pg/ml (22.9 ± 2.0 μU/ml), whereas maternal concentrations were not significantly elevated fetal plasma arginine vasopressin, 24.5 pg/ml (8.74 μU/ml).

Mean fetal plasma concentrations in the control period showed no changes during the control period. There was no change in any of these variables in the maternal blood as a result of the infusion.

Table 1

<table>
<thead>
<tr>
<th>Sheep</th>
<th>Gestational age (days)</th>
<th>Actual infusion rate (mU/min/kg)</th>
<th>Fetal plasma AVP</th>
<th>Maternal AVP</th>
<th>Time after start of infusion (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>134</td>
<td>*</td>
<td>4.1</td>
<td>101.9</td>
<td>2.2</td>
</tr>
<tr>
<td>2</td>
<td>137</td>
<td>*</td>
<td>4.3</td>
<td>87.5</td>
<td>0.5</td>
</tr>
<tr>
<td>3</td>
<td>123</td>
<td>*</td>
<td>5.4</td>
<td>74.5</td>
<td>1.9</td>
</tr>
<tr>
<td>4</td>
<td>124</td>
<td>*</td>
<td>5.2</td>
<td>41.0</td>
<td>2.1</td>
</tr>
<tr>
<td>5</td>
<td>140</td>
<td>*</td>
<td>0.91</td>
<td>65.3</td>
<td>5.4</td>
</tr>
<tr>
<td>6</td>
<td>140</td>
<td>*</td>
<td>1.6</td>
<td>25.4</td>
<td>0.8</td>
</tr>
<tr>
<td>7</td>
<td>124</td>
<td>1.36</td>
<td>2.6</td>
<td>165.4</td>
<td>2.4</td>
</tr>
<tr>
<td>8</td>
<td>125</td>
<td>1.23</td>
<td>5.8</td>
<td>83.6</td>
<td>2.8</td>
</tr>
<tr>
<td>9A</td>
<td>130</td>
<td>*</td>
<td>1.7</td>
<td>51.2</td>
<td>2.8</td>
</tr>
<tr>
<td>10</td>
<td>131</td>
<td>1.25</td>
<td>1.7</td>
<td>74.3</td>
<td>3.4</td>
</tr>
<tr>
<td>11†</td>
<td>123</td>
<td>1.29</td>
<td>24.5</td>
<td>54.3</td>
<td>7.7</td>
</tr>
<tr>
<td>12†</td>
<td>131</td>
<td>1.29</td>
<td>4.1</td>
<td>73.0</td>
<td>1.3</td>
</tr>
<tr>
<td>13†</td>
<td>132</td>
<td>1.29</td>
<td>4.1</td>
<td>73.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Mean</td>
<td>1.37</td>
<td>4.8</td>
<td>64.2†</td>
<td>3.2§</td>
<td>4.9§</td>
</tr>
<tr>
<td>SEM</td>
<td>0.11</td>
<td>1.17</td>
<td>5.66</td>
<td>0.70</td>
<td>0.75</td>
</tr>
</tbody>
</table>

* Not possible to determine actual infusion rate of vasopressin because fetal weights were not measured.
† Received infusion of synthetic arginine vasopressin. All other sheep received Pitressin.
§ Significantly different from control (P < 0.005).
$ Not significantly different from fetal control levels. Also, no significant difference between maternal levels during fetal infusion of vasopressin.

Blood Gases and pH
During vasopressin infusion, there were no significant changes in fetal blood osmolality, pH, PCO₂, or hematocrit (Table 2). Fetal femoral arterial PO₂ rose significantly as a result of vasopressin infusion from a resting level of 21.9 mm Hg to 24.1 mm Hg. There was no change in any of these variables in the maternal blood as a result of the infusion.

Heart Rate and Blood Pressure
The fetal heart rate and blood pressure responses to intravenous infusion of vasopressin are shown in Figure 1 and Table 2. The mean arterial blood pressure rose from an average of 47 ± 2 mm Hg to 56 ± 2 mm Hg (mean ± SEM). Systolic pressure rose from a mean of 65 ± 2 to 77 ± 2 mm Hg, whereas diastolic pressure rose from 38 ± 1 to 45 ± 2 mm Hg. The average time for the onset of the rise in blood pressure was 5.3 ± 1.1 minutes. The heart rate fell from a mean value of 174 ± 4 to 144 ± 4 beats/min. The average time for the onset of this response was 4.0 ± 0.4 minutes. The heart rate response preceded the rise in blood pressure in seven studies, in four studies the two responses occurred simultaneously, and in the other eight studies the rise in blood pressure preceded the fall in heart rate. Both these responses were maximal.
within 15 minutes after the onset of infusion and were maintained throughout the duration of the infusion.

Twin fetuses (9A and 9B) were studied separately. The blood pressure was monitored in both fetuses during infusion of vasopressin into fetus 9A. Fetus 9A responded with a rise in mean arterial blood pressure from 45 to 54 mm Hg and a fall in heart rate from 209 to 176 beats/min, whereas fetus 9B maintained a mean arterial blood pressure of 54 mm Hg and a stable heart rate. The plasma vasopressin concentration rose from 24.5 to 54.3 pg/ml in fetus 9A, and rose slightly from 3.4 to 5.4 pg/ml in fetus 9B. This suggests that vasopressin is not transferred from one fetus to another.

Plasma vasopressin concentrations, blood pressure, and heart rate were monitored for a period of up to 2 hours after termination of the infusion in eight fetuses. There was a decline in plasma arginine vasopressin in seven of the fetuses at times indicated in Table 3. The heart rate returned to control levels within a mean time of 23 minutes (range 7–39 minutes). Blood pressure fell more slowly toward control levels, requiring a mean time of 37 minutes (range 7–115 minutes).

The heart rate response to an intravenous injection of atropine (0.25 mg) was tested on three separate occasions to determine whether the bradycardia was a direct or a reflex action. Atropine had little effect on reversing the bradycardia, but this test was not conducted a sufficient number of times to allow statistical analysis.

### Combined Ventricular Output and Its Distribution

Table 4 shows the values of blood flows and fraction of combined ventricular output and vascular resistances before and during vasopressin infusion. The values during the control period are within the range of normal values for the appropriate gestational age, as previously reported (Rudolph and Heymann, 1970).

Mean combined ventricular output (Table 2) during vasopressin infusion was slightly lower than during the control period, but this difference was not significant. There was considerable change, however, in the distribution of cardiac output. The combined ventricular output delivered to the umbilical-placental circulation increased nearly 10%, from 40.9 ± 3.5% to 50.3 ± 4.0% (Table 4). There were similar increases in the proportion of combined ventricular output to the heart, spleen, and brain. Other vascular beds, such as the gut, peripheral circulation, thymus, and thyroid, received a decreased percent of the combined ventricular output. The actual blood flow (ml/min per 100 g wet weight of tissue) was also significantly decreased to the gut (30%), peripheral circulation (45%), thymus (36%), and thyroid (50%).
Vascular resistance, calculated as mean arterial pressure — central venous pressure/blood flow and expressed as ml/min per unit of weight, was changed in certain vascular beds during vasopressin infusion. Total peripheral resistance, including the umbilical-placental circulation, increased from 0.11 ± 0.01 to 0.15 ± 0.02 mm Hg/ml per min per kg fetal weight (Table 2). The total fetal body resistance excluding the umbilical-placental circulation showed a very marked increase, from 0.18 ± 0.02 to 0.33 ± 0.07. There were also significant increases in calculated resistances in the umbilical-placental, somatic, thymus, thyroid, heart, and gastrointestinal circulations (Table 4).

The dynamic changes in umbilical-placental blood flow were monitored with electromagnetic flow transducers in three fetuses. There was a decrease in blood flow (from 600 to 550 ml/min) to the placenta in one fetus concurrent with the fall in heart rate (from 173 to 143 beats/min) in response to the vasopressin infusion. The two other animals exhibited small increases in blood flow (from 610 to 680 and from 710 to 730 ml/min) despite a fall in heart rate. In both animals, there was a rise in mean arterial blood pressure (from 45 to 50 and from 39 to 47 mm Hg, respectively).

**Discussion**

We have found that resting concentrations of arginine vasopressin in the plasma of fetal lambs between 123 and 140 days gestation were 4.83 ± 1.17 pg/ml (1.73 ± 0.40 mU/ml); these were within the range of values reported by other investigators. Alexander et al. (1974b) failed to detect fetal plasma arginine vasopressin (less than 3.5 mU/ml, or about 10 pg/ml) in fetal lambs until a few days prior to parturition. Rurak (1975) reported undetectable (less than 5 mU/ml) or low (10 mU/ml, or 28 pg/ml) levels in his studies. Maternal plasma arginine vasopressin levels were not significantly different from fetal levels in these studies for fetuses of 121 to 141 days gestational age.

Intravenous infusion of Pitressin or synthetic arginine vasopressin at a rate of 0.9–2.3 mU/min per kg fetal weight raised fetal arginine vasopressin concentrations to a mean of 64.2 pg/ml (22.9 μU/ml). Although there was no significant elevation of arginine vasopressin concentration in the ewe dur-

### Table 3 Plasma Arginine Vasopressin (AVP) Concentrations in Fetuses after Cessation of Vasopressin Infusion

<table>
<thead>
<tr>
<th>Sheep</th>
<th>Gestational age (days)</th>
<th>Time before cessation of infusion (min)</th>
<th>Plasma AVP (pg/ml)</th>
<th>Time after cessation of infusion (min)</th>
<th>Plasma AVP (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>137</td>
<td>28</td>
<td>67.5</td>
<td>26</td>
<td>12.6</td>
</tr>
<tr>
<td>2</td>
<td>134</td>
<td>4</td>
<td>101.8</td>
<td>62</td>
<td>31.9</td>
</tr>
<tr>
<td>4</td>
<td>140</td>
<td>23</td>
<td>66.3</td>
<td>45</td>
<td>45.0</td>
</tr>
<tr>
<td>6</td>
<td>140</td>
<td>10</td>
<td>153.2</td>
<td>120</td>
<td>29.0</td>
</tr>
<tr>
<td>7</td>
<td>124</td>
<td>10</td>
<td>54.5</td>
<td>48</td>
<td>21.5</td>
</tr>
<tr>
<td>8</td>
<td>125</td>
<td>5</td>
<td>51.2</td>
<td>47</td>
<td>12.3</td>
</tr>
</tbody>
</table>

**All values are expressed as mean ± SEM.**

* P < 0.005.
† n = 7 for these organs due to technical difficulties in sample preparation; n = 8 for all other organs.
‡ Only considering hepatic arterial contribution of flow. Calculated resistance not indicative of total liver resistance.

### Table 4 Distribution of Combined Ventricular Output, Organ Blood Flows, and Vascular Resistances before and during Vasopressin Infusion

<table>
<thead>
<tr>
<th>% Combined Ventricular Output</th>
<th>Blood Flows (ml/min) 100 g</th>
<th>Vascular Resistance (mm Hg/ml per min per 100 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Infusion</td>
</tr>
<tr>
<td>Placenta</td>
<td>40.92 ± 3.47</td>
<td>50.30 ± 4.01*</td>
</tr>
<tr>
<td>Gut†</td>
<td>5.81 ± 0.80</td>
<td>4.57 ± 0.65*</td>
</tr>
<tr>
<td>Spleen†</td>
<td>1.10 ± 0.20</td>
<td>2.34 ± 0.20*</td>
</tr>
<tr>
<td>Adrenal†</td>
<td>0.08 ± 0.02</td>
<td>0.07 ± 0.02</td>
</tr>
<tr>
<td>Liver§</td>
<td>0.49 ± 0.19</td>
<td>0.67 ± 0.41</td>
</tr>
<tr>
<td>Kidneys</td>
<td>2.19 ± 0.23</td>
<td>2.94 ± 0.25</td>
</tr>
<tr>
<td>Thymus</td>
<td>0.79 ± 0.10</td>
<td>0.53 ± 0.10*</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.19 ± 0.08</td>
<td>0.14 ± 0.08*</td>
</tr>
<tr>
<td>Heart</td>
<td>3.00 ± 0.51</td>
<td>3.45 ± 0.68*</td>
</tr>
<tr>
<td>Brain</td>
<td>3.00 ± 0.41</td>
<td>4.09 ± 0.57*</td>
</tr>
<tr>
<td>Lungs</td>
<td>6.58 ± 0.93</td>
<td>7.19 ± 2.50</td>
</tr>
<tr>
<td>Peripheral circulation</td>
<td>34.55 ± 2.77</td>
<td>22.87 ± 3.04*</td>
</tr>
</tbody>
</table>
ing infusion, placental transfer of the hormone cannot be evaluated from the present data without measurement of the relative pool sizes of the fetus and mother and the distribution of arginine vasopressin within the animal. Our studies on the twin fetuses suggest that the hormone is not transferred from one fetus to the other.

The plasma concentrations of arginine vasopressin in the fetuses during infusion were within the range observed during fetal response to hemorrhage and hypoxia. A reduction of 5% fetal blood volume in sheep fetuses elevated plasma arginine vasopressin to 48 pg/ml, and to 200 pg/ml after removal of 10% blood volume. Hemorrhage of 20 ml/kg fetal weight caused a 15-fold rise in concentration of arginine vasopressin. A 40-50% reduction of blood volume in acutely exteriorized sheep fetuses elicited a maximal response of 80-1000 μU/ml (Alexander et al., 1974a). Maternal hypoxia caused an increase in sheep fetal arginine vasopressin concentration to 119 and 100 μU/ml (Alexander et al., 1972).

Sheep fetuses in utero responded to exogenous vasopressin with bradycardia that occurred before

\( v = 7 \), concomitant with \( v = 4 \), or after \( v = 8 \) a rise in blood pressure. Although Rurak (1975) also reported a bradycardia as a result of vasopressin infusion, he concluded that the decrease in heart rate was a reflex response that was abolished by vagotomy. In the present studies, injection of atropine into three fetuses resulted in no increase in heart rate in one fetus; in the other two, atropine produced a small increase, but the heart rate did not return to control levels. These observations suggest that the bradycardia response to vasopressin in the fetal lamb is partially a reflex response to the rise in blood pressure, but may also be due to a direct action on the heart.

Arginine vasopressin infusion produces bradycardia in adult animals as well. Studies in adult rabbits and dogs suggest that the bradycardia is partially, but not totally, due to a reflex response to the rise in blood pressure. Excision of the carotid sinus and section of the aortic nerve did not prevent the bradycardia in conscious rabbits (Youmans et al., 1952a). Vagotomy and carotid section reduced but did not abolish the response in conscious dogs (Younms et al., 1952b). A more recent study by Varma et al. (1969) showed that the bradycardia induced by vasopressin was only slightly attenuated by holding the arterial blood pressure constant, by vagotomy, by spinal cord section at C2, or by vagotomy combined with spinal cord section. In the same studies, intraventricular injection of vasopressin into either the lateral or the 4th ventricle elicited a profound bradycardia not affected by stabilizing the arterial blood pressure. Studies by Heyndrickx et al. (1976) in conscious dogs showed that vasopressin infusion produced bradycardia after complete denervation of the carotid sinus and aortic nerves. These studies in adult animals suggest that at least part of the action of vasopressin on the heart rate is directly on the heart as well as due to a reflex bradycardia.

The increase in blood pressure during infusion of vasopressin was the result of a direct vasoconstrictor action in certain vascular beds (Altura and Altura, 1977). There was a reduction of blood flow to the peripheral circulation and gut, an increase in the proportion of combined ventricular output to the placenta, heart, spleen, and brain, and an increase in vascular resistance in the umbilical-placental, peripheral, and coronary circulations. Studies in adult dogs have demonstrated similar responses to vasopressin. In conscious dogs studied with electromagnetic flowmeters (Heyndrickx et al., 1976), vasopressin infusion decreased flow through the coronary artery by 27%, through the mesenteric artery by 50%, and through the iliac artery by 60%, whereas it did not affect flow through the renal artery. Studies on anesthetized dogs (Schmid et al., 1974) showed a similar response as well as a significant reduction in flow to vascular beds in the muscles. The one difference between the studies in the fetal lamb and those in adult dogs was in relation to coronary blood flow. In the fetal lamb, we found an increase in the proportion of total flow to the heart, but no change in the actual blood flow despite an increase in vascular resistance. The increase in blood pressure or metabolic factors could account for the increase in the proportion of blood flow to the heart.

Although there was no change in the actual blood flow to the umbilical-placental circulation, there was an increase in the calculated vascular resistance. However, calculation of vascular resistance in the umbilical-placental circulation is unreliable when heart rate has changed (Rudolph, 1976). Vasopressin caused a bradycardia that would decrease blood flow to the placenta (Rudolph, 1976), whereas the increased blood pressure would increase placental flow. These two opposing hemodynamic changes apparently balanced one another during vasopressin infusion, resulting in no significant alteration of umbilical-placental blood flow. Vasopressin probably has no direct effect as a vasoconstrictor in the umbilical-placental circulation in the fetal lamb in utero.

It is clear from these studies that vasopressin has profound effects on the circulation of the fetal lamb at plasma concentrations that are comparable to those achieved during various types of stress. Changes in heart rate and blood pressure occur within a few minutes after the initiation of the infusion, are sustained during the infusion, and return to control levels after termination of the infusion. That there is a delay of 4-5 minutes in the onset of the changes in heart rate and blood pressure suggests that there is a critical plasma concentration of vasopressin that must be obtained before these changes become manifest.

Vasopressin may play a role in the fetal response to hypoxemia. Plasma concentrations of arginine
vasopressin in the fetus are increased in response to hypoxemia (Rurak, 1975; Alexander et al., 1972). Vasopressin in turn shifts blood flow from the peripheral and gastrointestinal vascular beds to the placenta, heart, brain, and spleen. The shift in blood flow is accompanied by a significant increase in oxygen concentration in fetal arterial blood. These are important adjustments to the fetus in terms of maintaining sufficient blood flow to the site of oxygenation and supplying adequate oxygen to vital organs. The distribution of combined ventricular output during fetal hypoxemia differs somewhat from the distribution during vasopressin infusion (Cohn et al., 1974). The proportion of combined ventricular output distributed to the placenta, coronary, and cerebral circulations increases in both instances. Vasopressin infusion causes a greater reduction in blood flow to the peripheral circulation and gut, whereas hypoxemia has no effect, although combined hypoxemia and acidemia result in a decrease in flow to these circulations (Cohn et al., 1974). Blood flow to the adrenals, kidneys, and lungs was not changed during vasopressin infusion, whereas hypoxemia significantly alters flow to these areas. In summary, it appears that, although vasopressin could play an important role in the fetal response to hypoxemia, it alone cannot fully account for the changes in the distribution of combined ventricular output manifest during hypoxemia.

Acknowledgments

The invaluable technical assistance of C. Roman, B. Payne, L. Wong, L. Williams, C. McWatters, and M. McCaw is gratefully acknowledged.

References

Keil LC, Severs WB: Reduction in plasma vasopressin levels of dehydrated rats following acute stress. Endocrinology 100: 30-38, 1977
Rudolph, AM: Factors affecting umbilical blood flow in the lamb in utero. Fifth European Congress of Perinatal Medicine, 1976, pp 159-172
Rurak DW: Plasma vasopressin in fetal lambs (abstr). J Physiol (Lond) 256: 36P-37P, 1975
Youmans WB, Good HV, Hewitt AF: Inhibitory effect of vasopressin on carodinoaccelerator mechanism after sino-aortic de-
Hemodynamic responses of the sheep fetus to vasopressin infusion.
H S Iwamoto, A M Rudolph, L C Keil and M A Heymann

Circ Res. 1979;44:430-436
doi: 10.1161/01.RES.44.3.430

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1979 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/44/3/430.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/