Renal responses to prolonged (48 h) hypoxemia without acidemia in the late-gestation ovine fetus

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Braaksma, Margriethe A., A. Carin M. Dassel, and Jan G. Aarnoudse. Renal responses to prolonged (48 h) hypoxemia without acidemia in the late-gestation ovine fetus. Am. J. Physiol. 277 (Regulatory Integrative Comp. Physiol. 46): R395–R402, 1999.—The effect of sustained moderate hypoxia on renal blood flow and renal function was studied in the ovine fetus (123–129 days). The experiments consisted of 48 h of isocapnic hypoxia, not resulting in acidemia, but sufficient to produce redistribution of blood flow in favor of the brain at the expense of the carcass. Hypoxemia was induced by maternal nitrogen inhalation. Fetal arterial O\textsubscript{2} saturation and arterial O\textsubscript{2} pressure (P\textsubscript{aO\textsubscript{2}}) decreased from, respectively, 50.6 ± 3.0% and 17.2 ± 0.9 mmHg during control to 36.4 ± 2.7% and 13.4 ± 0.7 mmHg on the first and to 32.2 ± 2.2% and 12.4 ± 0.7 mmHg on the second day of hypoxemia. Fetal renal blood flow and urine production rate were continuously measured using ultrasonic flow transducers. Fetal renal blood flow increased during hypoxemia from 11.8 ± 1.6 to 15.6 ± 1.8 ml/min and remained elevated throughout the 48-h hypoxemia period (P < 0.01). Renal blood flow was inversely correlated with fetal P\textsubscript{aO\textsubscript{2}} (r = −0.69, P < 0.0001). Fetal urine production rate, glomerular filtration rate, filtration factor, osmotic clearance, and free water clearance did not significantly change from control values during hypoxemia or recovery. We conclude that hypoxemia without acidemia results in an immediate and considerable increase in fetal renal blood flow, which remains elevated for the entire hypoxic period.

Fetal growth retardation (FGR) is of major clinical concern because there is a close relationship between the degree of growth retardation and perinatal morbidity and mortality (26). One of the causes of FGR is placental insufficiency, which is usually elevated by a decreasing amount of amniotic fluid, resulting in oligohydramnios. This is ascribed to a reduction in fetal urine flow, and it has been shown that the hourly urine production rate in the growth-retarded human fetus is reduced (28, 29). However, the mechanism leading to a diminished urine flow in the growth-retarded fetus is not yet understood. It has been suggested that the concomitant fetal hypoxemia, caused by placental insufficiency, causes a decrease in renal blood flow (1) due to redistribution of cardiac output in favor of the brain, heart, and adrenals (3, 23, 36). The decrease in renal blood flow would lead to reduced glomerular filtration and hence decreased fetal urine production and eventually to oligohydramnios (8).

In the human fetus, renal blood flow and urine production rate cannot be measured directly. With color Doppler-ultrasound, blood flow velocity waveforms of the renal arteries are used as an index of blood flow resistance downstream. Urine production rate is estimated from consecutive ultrasound measurements of bladder size. Ultrasound Doppler studies of blood flow in the renal artery in the human growth retarded fetus show conflicting results (1, 29), and data on fetal urine production rate are not univocal (28, 31).

In the ovine fetus, renal blood flow and urine production rate can be measured directly and continuously. Furthermore, whereas urine production rate in the human fetus is found to depend on behavioral states (30), in the ovine fetus no relation was found between urinary blood flow rate and high- or low-voltage electrocortical activity (5). Therefore, fetal renal responses to hypoxemia can be much more accurately studied in the sheep fetus than in the human fetus.

Although human FGR is associated with chronic moderate hypoxia (3), most animal studies concern the fetal renal responses to acute hypoxia. In those studies, hypoxia is often severe and accompanied by acidemia (35). Moreover, the results of those studies are conflicting. The studies in which microspheres were used showed a decrease in renal blood flow (33, 37), whereas those in which electromagnetic flow probes were used showed an increase (27). Also, results concerning ovine fetal urine production rate during hypoxemia are conflicting. Depending on the severity of hypoxia and the way it was applied, a decrease or an increase or no change in fetal urine flow has been reported (11, 40).

The lack of chronic hypoxia studies prompted us to investigate the effect of sustained moderate hypoxia on renal blood flow and renal function in the near-term ovine fetus. The experiments consisted of 48 h of isocapnic hypoxia, not resulting in acidemia, but sufficient to produce redistribution of blood flow in favor of the brain at the expense of the carcass. Renal blood flow and urine production rate were continuously measured by means of ultrasonic flow transducers.

MATERIAL AND METHODS

Surgical Procedures

Studies were carried out in 15 fetal sheep of mixed breed between 123 and 129 days gestation (term 147 days). Surgical procedures were performed at least 6–7 days before the initiation of the measurements. Food but not water was withheld for 16 h before surgery. General anesthesia was induced by intravenous diazepam (1 mg/kg), ketamine (10 mg/kg), and glycopyrulate (0.4 mg). The ewe was intubated...
and mechanically ventilated and anesthesia was maintained with ketamine (14 mg/min iv) and halothane (0.5-2.0%) in oxygen. The uterus was exposed and opened through a paramedian incision in the lower abdomen. Fetal hindlimbs and abdomen were exteriorized, after which polyvinyl chloride catheters were inserted in the fetal left femoral vein and both left and right femoral arteries for blood sampling, administration of antibiotics, and for continuous recording of arterial blood pressure. Through a paravertebral incision, the right renal artery was carefully exposed and an ultrasonic flow-transducer (Transonic Systems) was placed around the right renal artery. Care was taken not to kink or occlude the artery by choosing a transducer size with a loose fit to the artery (25 or 35 transducers). A closed tip catheter was inserted via a small abdominal incision in the bladder (gastro-duodenal feeding tube 391.16, Vygon, Veenendaal, The Netherlands). The urethra and urachus were ligated to ensure all produced urine was collected. The fetus was then returned to the uterus, which was closed in layers. In four fetal lambs, a second uterine incision was made, and the fetal head and forelimbs were exteriorized. An ultrasonic blood flow transducer (35 or 45) was placed on the left and right carotid arteries in these animals.

Two double-lumen catheters were placed in the amniotic cavity for continuous recording of intra-amniotic pressure and to return the collected fetal urine. After the uterus was closed, two pairs of Teflon-insulated stainless steel wire electrodes (N12-50F-405-0, New England Wire, Lisbon, NH) were sewn in the myometrial wall to record electromyo-graphic activity. Maternal catheters were placed in the left femoral artery and vein for blood sampling and administration of antibiotics. All catheters and leads were tunneled to the ewe's left flank, and the abdominal wall was closed. A small catheter was implanted in the ewe's trachea for administration of nitrogen during the hypoxia studies.

After surgery, 500 ml of warm Ringer lactate was infused into the amniotic cavity to replenish the lost amniotic fluid. Before and after surgery, antibiotics [cefuroxime (Zinacef), Glaxo, Zeist, the Netherlands] were given to the ewe and the fetus (1,200 mg iv to the ewe, 100 mg iv to the fetus, and 200 mg into the amniotic cavity). Analgesics were administered to the fetus (1,200 mg iv to the ewe, 100 mg iv to the fetus, and 200 mg into the amniotic cavity). Maintenance catheters were placed in the left femoral artery (2S or 3S transducers). A closed tip catheter was inserted via a small abdominal incision in the bladder (gastro-duodenal feeding tube 391.16, Vygon, Veenendaal, The Netherlands). The urethra and urachus were ligated to ensure all produced urine was collected. The fetus was then returned to the uterus, which was closed in layers. In four fetal lambs, a second uterine incision was made, and the fetal head and forelimbs were exteriorized. An ultrasonic blood flow transducer (35 or 45) was placed on the left and right carotid arteries in these animals.

Physiological Measurements

At least 6 ± 1 days of postsurgical recovery were allowed before experiments began. Measurements were performed during 4 consecutive days: during control conditions, 48 h of moderate hypoxia, and during recovery after hypoxia. Hypoxia was induced by delivering N2 (4.5–5.5 l/min) by the tracheal catheter to the ewe. To prevent maternal hypocapnia due to hyperventilation, CO2 (50–100 ml/min) was given to the ewe during hypoxemia. The induction of fetal hypoxia, measuring 60–70% of the fetal prehypoxia SaO2 level, indicated the N2 dose delivered to the ewe. During the control and the recovery period, air was delivered to the ewe by the tracheal catheter (5.0 l/min).

Blood gas analysis was performed at hourly intervals and more frequently (every 15–30 min) during the induction of hypoxia. Each day, recordings were made for 6 h between 0830 and 1600. Control, hypoxemia, and recovery measurements were made on consecutive days. Fetal renal blood flow, carotid blood flow, arterial blood pressure, fetal heart rate, fetal urine production rate, and intra-amniotic pressure were measured continuously. All signals were recorded on an eight-channel recorder (Gould, model 8188, Cleveland, OH) and also stored on disk in an online computer system (Polyms Research, Amsterdam, The Netherlands) at a sampling rate of 10 Hz.

Glomerular filtration rate (GFR) was determined by using polyfructosan (Inutest, Bournville, Almere, The Netherlands). At the start of the daily 6-h measurement period, a priming dose of polyfructosan (25 mg/ml) in isotonic saline was infused for 20 min at a rate of 26.67 ml/h, followed by a maintenance dose of polyfructosan (25 mg/ml) at a rate of 6.67 ml/h for the remaining time of the daily measurement. An equilibration period of 3 h was allowed for the compounds to reach steady-state plasma concentration. Then, three 1-h urine collections were made with midpoint blood samples. Urine and plasma osmolality were determined by freezing-point depression (Osmomat 030 Gonotec, Salm & Kipp, Breukelen, The Netherlands), and serum and urine samples were stored at −20°C until analysis. The anthrone method (16) was used to measure polyfructosan in serum and urine. GFR and filtration fraction (FF) were calculated with standard formulae.

At the end of the daily 6-h measurement, fetal plasma was taken and stored at −80°C until catecholamines were measured, using reversed phase chromatography and electrochemical detection (38).

At the end of experiments the animals were killed by overdose of pentobarbital sodium. The ultrasonic flow probes were checked for their zero flow value, and experimental flow data were corrected if necessary. Fetuses were towel-dried, weighed, placement of catheters was verified, and kidneys were removed and weighed.

Data and Statistical Analysis

All results are presented as means ± SE. Computer-stored data were averaged over 3 min before analysis. Statistical significance was determined by either Wilcoxon's matched-
pairs test with Bonferroni correction, analysis of variance, or linear correlations, when appropriate. A probability level of \( P < 0.05 \) was taken as statistical significance.

**RESULTS**

During the control period, fetal arterial blood gas values were within the normal ranges usually obtained in our laboratory (42) and in agreement with other studies (37). Fetal body weight at autopsy was 2.7 ± 0.1 kg, and total kidney weight was 24.7 ± 2.1 g, with no significant difference between the instrumented right kidney and the left kidney.

**Fetal Blood Gas and Circulatory Responses to Hypoxemia**

Nitrogen administered to the ewe induced a decrease in fetal \( \text{SaO}_2 \) and \( \text{PaO}_2 \) from 50.6 ± 3.0% and 17.2 ± 0.9 mmHg, respectively, during control, to 36.4 ± 2.7% and 13.4 ± 0.7 mmHg on the first day and to 32.2 ± 2.2% and 12.4 ± 0.7 mmHg on the second day of hypoxemia (Table 1). Replacement of nitrogen with air, after 48 h of hypoxia, resulted in good recovery of the blood gas values. Fetal \( \text{PaCO}_2 \) levels did not change significantly during the 48 h of hypoxia, whereas pHa slightly decreased during the second part of the 48 h of hypoxia from 7.33 ± 0.01 to 7.30 ± 0.02. Although this decrease reached significance (\( P < 0.01 \)), there was no progressive acidemia except for one fetus. During the recovery period, \( \text{PaCO}_2 \) slightly increased and pHa decreased. No significant changes in fetal arterial base excess were observed during the 48 h of hypoxemia, but a slight but significant decrease was found during the recovery period (\( P < 0.05 \)). The fetal blood gas data are summarized in Table 1. Fetal arterial blood pressure and fetal heart rate did not change during hypoxia (Fig. 1, Table 1) but tended to decrease during the recovery period, when fetal heart rate was significantly lower compared with the control values.

Fetal carotid blood flow, which was measured in four animals, was significantly increased during the entire hypoxia period, from 65.4 ± 2.4 to 85.6 ± 8.5 ml/min (\( P < 0.01 \)), and returned to prehypoxic levels during the recovery period (61.1 ± 3.5 ml/min). The increase in fetal carotid blood flow was significantly correlated with the decrease in fetal \( \text{PaO}_2 \) (\( r = -0.71, P < 0.01 \), Fig. 2).

**Fetal Renal Responses to Hypoxemia**

Renal blood flow. Renal blood flow showed considerable “spontaneous” fluctuations during the control period. During hypoxia, renal blood flow increased significantly compared with the control values, from 11.8 ± 1.6 to 15.6 ± 1.8 ml/min (Fig. 1). Corrected for kidney weight, fetal renal blood flow per gram kidney tissue also increased significantly during hypoxemia, whereas renal vascular resistance (RVR) showed a significant decrease, from 2.2 ± 0.3 to 1.6 ± 0.2 mmHg·min⁻¹·ml⁻¹

<table>
<thead>
<tr>
<th>Table 1. Fetal arterial responses to hypoxemia</th>
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<tr>
<td></td>
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<tr>
<td><strong>Control</strong></td>
</tr>
<tr>
<td>( \text{SaO}_2 ), %</td>
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<tr>
<td>( \text{PaO}_2 ), mmHg</td>
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<tr>
<td>( \text{PaCO}_2 ), mmHg</td>
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<td>pHa</td>
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<tr>
<td>Base excess</td>
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<tr>
<td>MAP, mmHg</td>
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<td>FHR, beats/min</td>
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<td>Q a. carotis, ml/min</td>
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Values are means ± SE. \( \text{SaO}_2 \), arterial \( \text{O}_2 \) saturation; \( \text{PaO}_2 \); and \( \text{PaCO}_2 \), arterial pressure of \( \text{O}_2 \) and \( \text{CO}_2 \), respectively; pHa, arterial pH; MAP, mean arterial pressure; FHR, fetal heart rate; Q a. carotis, blood flow arteria carotis. * \( P < 0.05 \), Wilcoxon’s matched pairs test vs. control conditions.

Renal oxygen delivery. During the first 24 h of hypoxemia, renal oxygen delivery was maintained (7.4 ± 1.3 and 6.9 ± 1.7 ml·min⁻¹·100 g⁻¹ during control and hypoxemia day 1, respectively), but during the second 24 h of hypoxemia, oxygen delivery (5.8 ± 1.1 ml·min⁻¹·100 g⁻¹) was significantly decreased compared with the control period (\( P < 0.01 \)).

Renal function. The osmotic clearance (\( \text{Cosm} \)) and free water clearance (\( \text{Ch}_{\text{H}_2\text{O}} \)) did not change significantly during the 48 h of hypoxemia nor during the recovery period.

Catecholamines. Fetal plasma epinephrine and norepinephrine levels were measured in six animals. Compared with control values, plasma epinephrine increased in the 48 h of hypoxemia from 263 ± 168 to 377 ± 217 pg/ml and plasma norepinephrine increased from 520 ± 313 to 971 ± 547 pg/ml, but the difference did not reach significance.
DISCUSSION

Our findings indicate that prolonged fetal hypoxemia, of a degree not resulting in acidemia and/or a change in fetal PaCO₂, causes an immediate and sustained increase in renal blood flow, whereas fetal urine production rate remains almost unchanged. These observations were made in the near-term chronically instrumented fetal sheep, which provides a convenient and generally accepted model for examining the circulatory and renal responses to hypoxemia (4). However, when investigating the renal responses, the slow recovery of fetal renal function from the stress of surgery has to be taken in consideration. We and others (17) experienced that recovery of renal function takes ~5 days, and therefore we did not start measurements until 6–7 days after surgery.

In the present study we induced moderate fetal hypoxia for 48 h, with virtually no changes in blood acid base balance, but sufficient to cause redistribution of cardiac output. The level of hypoxemia achieved in the present study was associated with a considerable increase in common carotid artery flow, indicating a substantial increase in blood flow to the fetal brain (39). Redistribution of blood flow in favor of the fetal brain occurs at the expense of peripheral organs (23). Indeed, in a previous study in fetal lambs we found at a similar degree of hypoxemia, a decrease in abdominal aorta blood flow of 16% with a concomitant increase in fetal common carotid blood flow of 31%, using the same ultrasonic blood flow technique (unpublished results).

It is commonly believed that the fetal hypoxic response of a reduced peripheral blood flow includes the
were seen in pHa and PaCO2 compared with normoxemia. In those fetal sheep renal oxygen delivery decreased in renal artery blood flow during fetal hypoxemia, which remained elevated for the entire 48 h of hypoxia. Furthermore, a strong inverse correlation was found between fetal PaO2 and renal blood flow (12). A similar correlation has been reported by Iwamoto and Rudolph (21) in fetal lambs that were spontaneously hypoxic. They also found an increase in renal blood flow when arterial O2 content decreased spontaneously hypoxic. In fetal sheep renal oxygen delivery was maintained, a phenomenon that was also apparent in the present study, albeit only for the first 24 h of hypoxemia. During these initial 24 h of hypoxemia, we found no changes in renal function, whereas in the second 24-h period of hypoxemia, when renal oxygen delivery became significantly reduced, both GFR and FF decreased.

Our results seem at variance with the concept that fetal hypoxemia is associated with diminished renal blood flow. However, the appreciation of the fetal renal response to hypoxemia is complicated by the various techniques and experimental conditions employed (35). Fetal hypoxemia can be induced by occlusion of the umbilical cord, by reducing blood flow to the uterine arteries, by embolization of the placenta, or by lowering the inhaled oxygen concentration of the ewe. Factors beside fetal hypoxemia, such as acidemia and hypercapnia, can have specific influences on fetal renal function. The use of different techniques yields different degrees of fetal hypoxemia with variable combinations of acidemia and hypercapnia.

In the present study there was neither progressive acidemia nor hypercapnia, which made it possible to study the effects of almost pure hypoxemia on fetal renal blood flow without all the concomitant changes that are usually associated with hypoxemia studies in the sheep fetus. Another difference between former studies on the renal response of the fetus to hypoxia and the present study is the continuous blood flow measurement we used instead of the use of microspheres. Although a well-established method, an essential limitation of the microsphere method is the intermittent character of the technique and the restricted number of observations. Continuous measurement offers the online ability to recognize rapid changes in blood flow immediately during the entire observation period. Hitherto, only two studies on ovine fetal renal blood flow during acute hypoxemia have been reported where continuous measurement techniques were used (13, 27). It is striking that in those two acute studies, an increase in fetal renal blood flow was also observed. Chronic hypoxemia studies using continuous measurement techniques have not been reported in the ovine fetus.

Why most of the studies using microspheres found the opposite effect remains unknown, but may be at

Table 2. Fetal urine flow and renal responses during various measurements

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine flow, ml/min</td>
<td>0.56 ± 0.06</td>
<td>0.63 ± 0.10</td>
<td>0.55 ± 0.07</td>
<td>0.65 ± 0.16</td>
</tr>
<tr>
<td>Urine flow, ml·min⁻¹·g kidney wt⁻¹</td>
<td>0.025 ± 0.003</td>
<td>0.028 ± 0.004</td>
<td>0.027 ± 0.004</td>
<td>0.030 ± 0.008</td>
</tr>
<tr>
<td>GFR, ml/min</td>
<td>1.81 ± 0.22</td>
<td>1.62 ± 0.20</td>
<td>1.40 ± 0.31</td>
<td>1.72 ± 0.48</td>
</tr>
<tr>
<td>GFR, ml·min⁻¹·g kidney wt⁻¹</td>
<td>0.074 ± 0.006</td>
<td>0.071 ± 0.008</td>
<td>0.065 ± 0.014</td>
<td>0.068 ± 0.015</td>
</tr>
<tr>
<td>Osmolality, mosmol/kgH2O</td>
<td>156 ± 8</td>
<td>171 ± 15</td>
<td>151 ± 12</td>
<td>147 ± 10</td>
</tr>
<tr>
<td>FF, %</td>
<td>9.4 ± 1.6</td>
<td>6.9 ± 1.1</td>
<td>5.6 ± 1.2</td>
<td>8.2 ± 3.4</td>
</tr>
<tr>
<td>Renal oxygen delivery, ml·min⁻¹·100 g⁻¹</td>
<td>7.4 ± 1.3</td>
<td>6.9 ± 1.7</td>
<td>5.8 ± 1.1*</td>
<td>9.0 ± 2.5</td>
</tr>
<tr>
<td>Qa, renalis, ml·min⁻¹·g kidney wt⁻¹</td>
<td>0.98 ± 0.13</td>
<td>1.23 ± 0.16*</td>
<td>1.27 ± 0.14*</td>
<td>1.18 ± 0.17</td>
</tr>
<tr>
<td>RVR, mmHg·min⁻¹·ml⁻¹</td>
<td>2.2 ± 0.3</td>
<td>1.7 ± 0.2*</td>
<td>1.6 ± 0.2*</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>Csm, ml/min</td>
<td>0.35 ± 0.07</td>
<td>0.32 ± 0.06</td>
<td>0.34 ± 0.07</td>
<td>0.38 ± 0.12</td>
</tr>
<tr>
<td>CH2O, ml/min</td>
<td>0.27 ± 0.03</td>
<td>0.27 ± 0.06</td>
<td>0.33 ± 0.05</td>
<td>0.31 ± 0.07</td>
</tr>
</tbody>
</table>

Values are means ± SE. GFR, glomerular filtration rate; FF, filtration fraction; RVR, renal vascular resistance; Csm, osmotic clearance; CH2O, free water clearance.*P < 0.05 vs. control, Wilcoxon’s matched pairs test with Bonferroni correction.
least partly explained by essential differences between the methods: the continuous ultrasonic and electromagnetic methods measure the blood flow in the artery supplying the kidney, whereas the microsphere technique uses only the microspheres trapped in the microvessels of the kidney to assess blood flow. During hypoxemia, redistribution of intrarenal blood flow takes place in favor of the inner medulla, because this area is highly vulnerable to hypoxemia (14). Blood flow to the renal medulla is derived mainly from the efferent arterioles of the juxtamedullary glomeruli. The increase in medullary blood flow will be underestimated by the usually applied microsphere technique (32). This is partly explained by the separation of red blood cells from the plasma somewhere between the renal artery and the medullary circulation (18, 32), a process called “plasma skimming.”

Theoretically, the observed differences between the microsphere and the Transonic method could also be the result of a deleterious effect of the probe on the innervation of the kidney. Direct stimulation of the renal nerves produces a decrease in renal blood flow and an increase in renal vascular resistance (34). After renal denervation, there is an early vasodilatory response to hypoxemia (−10 min in duration) followed by progressive vasoconstriction (33), and sympathectomy resulted in no change in blood flow to the fetal kidneys during hypoxemia (23). Therefore, it is unlikely that the observed increase in fetal renal blood flow is caused by damage to the renal nerve.

Two fetal lambs did not recover from hypoxemia and showed progressively decreasing PaO2 levels, although the ewes fully recovered. In these animals, fetal renal blood flow did not decrease during recovery to the control level but increased further. Within 24 h after replacing the nitrogen administration to the ewe with air, parturition started and blood flow recording of the fetal renal arteries became impossible.

How does hypoxemia increase renal blood flow in the fetus? Because the fetal arterial blood pressure did not change during the hypoxemia period, we conclude that the increase in fetal renal blood flow is not due to increased renal perfusion pressure, but more likely is due to changes in the resistance within the kidney. This may be achieved by local and systemic responses to hypoxemia. Acute hypoxemia results in activation of the fetal neuroendocrine system, including the hypothalamic-pituitary-adrenal axis, resulting in increased fetal plasma concentrations of catecholamines (33, 35), plasma arginine vasopressin (1, 33, 35), atrial natriuretic factor (7), adrenocorticotropic hormone (6), plasma renin (33), and cortisol (6). During prolonged hypoxemia, however, many of the endocrine changes are not sustained (19). Plasma cortisol and norepinephrine levels remain elevated, but only during severe hypoxemia accompanied by hypercapnia and transient...
or more pronounced acidemia (6, 19, 20). Cortisol is known to increase renal blood flow, but only in high concentrations (12). Mild to moderate hypoxemia (~20% saturation decrease) without acidemia does not seem to be an adequate stimulus to increase catecholamines (24), an observation that was confirmed in the present study, whereas isocapnic hypoxia does not change fetal plasma renin activity (41).

Prostaglandins have been implicated in the regulation of renal blood flow, especially to the medulla of the kidney, and the medulla is known to contain high levels of these hormones (32). During sustained hypoxemia, prostaglandin E2 remains elevated for the entire hypoxic period (20). Furthermore, blood flow to the medulla of the rat kidney after administration of the prostaglandin synthesis inhibitor indomethacin was reduced (14). Another vasodilator with direct action on the renal medulla is adenosine (32), which is increased during hypoxemia (25) and particularly improves vasa recta flow (14). Nitric oxide (NO), produced from arginine by NO synthase, which is heavily concentrated in the renal medulla, also increases medullary blood flow (14). Because hypoxemia is a potent stimulator for the release of NO (2), this vasodilator could influence the vascular tone especially in the renal microcirculation (16).

The effect of hypoxemia on fetal urine production rate has been studied in a number of sheep experiments. The results of these studies are inconsistent, probably due to differences in the methods used to induce hypoxia and the duration and the severity of the hypoxia. Acute fetal hypoxemia caused fetal urinary output to decrease (35), whereas longer periods of hypoxemia start off with an antidiuresis followed by normal levels of urine production after 6 h (40). Reducing uterine blood flow to induce fetal hypoxemia resulted in an increase in urine production rate (11, 40).

During acute hypoxemia, the fall in urine flow is accompanied by a decrease in fetal GFR, FF, and C H2O, whereas urine osmolality and C osm increase (33, 35). In the present study, however, we have shown that chronic mild to moderate hypoxemia without changes in pHa and PaCO2 does not induce significant changes in fetal urine production rate, GFR, FF, C osm, or C H2O. Also, no transient changes in urine output were found at the onset of hypoxemia, the period that can be considered as an acute hypoxic event. Although we did not study GFR, FF, and C osm in the period immediately after the onset of hypoxemia, after 3 h of hypoxemia no changes were found in GFR, FF, and C osm compared with control values. Our findings are in agreement with the results of recent studies by Cock et al. (9, 10), who also found no changes in fetal urine production or GFR during prolonged hypoxemia in the absence of acidemia in the ovine fetus. All these findings suggest that the decreased urine production rate that has been observed in the human growth-retarded fetus (28, 31) is not the result of hypoxemia per se.

We speculate that the sustained increase in renal blood flow during 48 h of moderate hypoxemia protects the vulnerable areas of the fetal kidney to ischemic-hypoxic damage, because normal fetal renal blood flow is already significantly lower than in the adult.

Perspectives

From the results of the present study and those of others, there is convincing evidence now that urine production rate is not reduced during sustained pure hypoxemia without acidemia. Therefore, the decrease in fetal urine flow and the decrease in amniotic fluid observed in the growth-retarded fetus have to be explained by other factors associated with undernutrition in utero. Future studies should focus on the mechanisms that cause decreased urine flow and oligohydramnios under these circumstances. The role of fetal swallowing, lung liquid production, and transmembranal fluid transfer as well as the specific alterations in renal function should be investigated in the malnourished fetus.

Future studies should also concentrate on the possible deleterious effects of the hypoxemia-induced increase in renal blood flow in the chronic hypoxic fetus, which considerably exceeds the relatively low normal blood flow to the kidney in the fetus (compared with renal blood flow in the postnatal situation). It could be possible that a chronic increase in renal blood flow during fetal life definitely influences the setpoint or programming of receptors involved in the regulation of circulation. This might be a mechanism explaining the observed association between undernutrition in utero and hypertension and cardiovascular disease in adult life.

We thank Jan Elstrodt for animal technical assistance and Dr. Dick de Zeeuw for advice in study setup with regard to renal function. We also thank Robert de Vrij and Gerdien de Korte for, respectively, polyfructosan and catecholamine analyses. Finally, thanks are due to Drs. G. J. Navis and W. G. Zijlstra for critically reading the manuscript.

The antibiotics (Zinacef) used in this study were kindly donated by Glaxo, Zeist, The Netherlands. The polyfructosan (Inutest) was kindly donated by Bournoville, Almere, The Netherlands. The prostaglandin E2 remained elevated for the entire hypoxic period (20). Furthermore, blood flow to the medulla of the rat kidney after administration of the prostaglandin synthesis inhibitor indomethacin was reduced (14). Another vasodilator with direct action on the renal medulla is adenosine (32), which is increased during hypoxemia (25) and particularly improves vasa recta flow (14). Nitric oxide (NO), produced from arginine by NO synthase, which is heavily concentrated in the renal medulla, also increases medullary blood flow (14). Because hypoxemia is a potent stimulator for the release of NO (2), this vasodilator could influence the vascular tone especially in the renal microcirculation (16).

The effect of hypoxemia on fetal urine production rate has been studied in a number of sheep experiments. The results of these studies are inconsistent, probably due to differences in the methods used to induce hypoxia and the duration and the severity of the hypoxia. Acute fetal hypoxemia caused fetal urinary output to decrease (35), whereas longer periods of hypoxemia start off with an antidiuresis followed by normal levels of urine production after 6 h (40). Reducing uterine blood flow to induce fetal hypoxemia resulted in an increase in urine production rate (11, 40).

During acute hypoxemia, the fall in urine flow is accompanied by a decrease in fetal GFR, FF, and C H2O, whereas urine osmolality and C osm increase (33, 35). In the present study, however, we have shown that chronic mild to moderate hypoxemia without changes in pHa and PaCO2 does not induce significant changes in fetal urine production rate, GFR, FF, C osm, or C H2O. Also, no transient changes in urine output were found at the onset of hypoxemia, the period that can be considered as an acute hypoxic event. Although we did not study GFR, FF, and C osm in the period immediately after the onset of hypoxemia, after 3 h of hypoxemia no changes were found in GFR, FF, and C osm compared with control values. Our findings are in agreement with the results of recent studies by Cock et al. (9, 10), who also found no changes in fetal urine production or GFR during prolonged hypoxemia in the absence of acidemia in the ovine fetus. All these findings suggest that the decreased urine production rate that has been observed in the human growth-retarded fetus (28, 31) is not the result of hypoxemia per se.

We speculate that the sustained increase in renal blood flow during 48 h of moderate hypoxemia protects the vulnerable areas of the fetal kidney to ischemic-hypoxic damage, because normal fetal renal blood flow is already significantly lower than in the adult.

Perspectives

From the results of the present study and those of others, there is convincing evidence now that urine production rate is not reduced during sustained pure hypoxemia without acidemia. Therefore, the decrease in fetal urine flow and the decrease in amniotic fluid observed in the growth-retarded fetus have to be explained by other factors associated with undernutrition in utero. Future studies should focus on the mechanisms that cause decreased urine flow and oligohydramnios under these circumstances. The role of fetal swallowing, lung liquid production, and transmembranal fluid transfer as well as the specific alterations in renal function should be investigated in the malnourished fetus.

Future studies should also concentrate on the possible deleterious effects of the hypoxemia-induced increase in renal blood flow in the chronic hypoxic fetus, which considerably exceeds the relatively low normal blood flow to the kidney in the fetus (compared with renal blood flow in the postnatal situation). It could be possible that a chronic increase in renal blood flow during fetal life definitely influences the setpoint or programming of receptors involved in the regulation of circulation. This might be a mechanism explaining the observed association between undernutrition in utero and hypertension and cardiovascular disease in adult life.

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