Prostaglandin Control of the Renal Circulation in Response to Hypoxemia in the Fetal Lamb in Utero

RONALD W. MILLARD, HANK BAIG, AND STEPHEN F. VATNER

SUMMARY We studied the effects of 10-minute periods of hypoxemia in unanesthetized fetal lambs in utero instrumented for measurements of arterial pressure and renal and iliac blood flows. Fetal hypoxemia, induced by delivering a hypoxic gas mixture to the ewe, was characterized by a reduction in fetal Pao2 from 20.1 ± 1.4 to 8.8 ± 1.0 mm Hg (mean ± se). The fetus responded with bradycardia and persistent vasoconstriction in the iliac bed throughout the 10-minute period. In contrast, renal resistance rose significantly only at the end of the hypoxemic period. After 5–7 minutes of hypoxemia, when iliac flow had fallen by 40 ± 4% and iliac resistance had risen by 86 ± 13%, renal flow and resistance were not changed significantly from control; in fact, we found that renal flow rose substantially at this time in several fetal lambs. After blockade of prostaglandin synthesis with either indomethacin or meclofenamate, renal flow fell after 5–7 minutes of hypoxemia by 36 ± 5%. The reduction in renal flow and increases in renal resistance were significantly greater than was observed prior to blockade of prostaglandin synthesis. Thus, fetal hypoxemia elicits bradycardia and intense peripheral vasoconstriction reflected by the changes in the iliac bed, with relative sparing of the renal bed. The relative protection of the renal bed during fetal hypoxemia appears to be related to a mechanism involving prostaglandins, since after blockade of prostaglandin synthesis, hypoxemia results in intense renal vasoconstriction. Circ Res 45:173–179, 1979

ONE of the primary compensatory adjustments to fetal hypoxemia is sympathetic peripheral vasoconstriction (Assali et al., 1962; Campbell et al., 1967; Cohn et al., 1974). By this mechanism, blood flow to less essential organs is reduced, preserving blood flow to the brain and heart. The primary goal of this investigation was to determine the time course and extent of vasoconstriction in the renal circulation induced by hypoxemia in unanesthetized fetal lambs. These effects were compared with those in a relatively nonessential bed, i.e., the iliac. The second goal was to determine if sympathetically mediated renal vasoconstriction, induced by hypoxemia, might be attenuated by local prostaglandin mechanisms, as has been shown to occur in adult animals in response to hemorrhage (Vatner, 1974), renal nerve stimulation (Dunham and Zimmerman, 1970) or infusion of vasoconstrictors (Aiken and Vane, 1973; Lonigro et al., 1973; McGiff et al., 1972; Swain et al., 1975), or to renal hypotension (Herbaczynska-Cedro and Vane, 1973). These goals were attained by examining direct and continuous measurements of renal and iliac blood flows and arterial pressure in instrumented fetal lambs in utero in response to hypoxemia induced in the ewe. The fetal renal vascular response to hypoxemia was examined in both the presence and absence of inhibition of prostaglandin synthesis with meclofenamate or indomethacin.

Methods

Pregnant ewes of mixed breeds with fetuses of gestational ages from 125 to 140 days were anesthetized with sodium thiopental (sodium thiamylal, 10 mg/kg, iv) for induction, intubated and maintained at a surgical level of anesthesia with 1.0 to 1.5% halothane mixed with 100% oxygen. Under aseptic conditions, a catheter was inserted in the maternal femoral artery. The uterus was exposed through a mid-ventral abdominal incision and the fetus was located by palpation. The hind quarters of the fetus were withdrawn from the uterus through a hysterotomy in the uterine horn without significant loss of amniotic fluid. Catheters (polyvinyl chloride, 0.07 inches × 0.04 inches) were inserted via the femoral artery and vein so that the tips lay in the mid-abdominal aorta and vena cava, respectively. The venous catheter was used to inject drugs, as well as to measure pressure, and the arterial catheter was used to measure pressure, as well as to sample blood for arterial blood gas analysis. A catheter also was implanted in the amniotic cavity to measure intrauterine pressure. Doppler or electromagnetic flow transducers (2–2.5 mm i.d.) were placed around the contralateral iliac artery and the left renal artery via a retroperitoneal flank incision. The Doppler
ultrasonic flow transducers were fabricated in this laboratory and were chosen carefully at the time of surgery to match vessel external diameter closely. The electromagnetic flow transducers are commercially available units (Zepeda Instruments) and again were chosen at the time of implantation to optimize the match with vessel size. The fetus was returned to the uterus after closure of the three incision sites and the hysterotomy was repaired. The maternal laparotomy was closed by three suture layers. All catheters and flow transducer wires were threaded subcutaneously in the ewe to emerge in the lateral flank, where they were secured in a small fabric pouch. Antibiotics were administered as follows: kanamycin, 500 mg, im, to the fetus at operation, 2 g, im, to the ewe daily; Combiotic (penicillin-streptomycin) to the ewe daily, 2 × 10⁶ units, im.

Maternal and fetal arterial pressures, fetal venous pressure, and intrauterine pressure were measured using Statham P23Db strain gauge manometers. The Doppler ultrasonic flowmeter was used to measure renal blood flow in nine fetuses. In six of these, iliac blood flow also was measured. The continuous-wave Doppler flowmeter used was constructed in this laboratory and uses a carrier frequency of 9.7-9.9 MHz. An important feature of this flow system is the accurate electrical zero reference, which does not require occlusion of the vessel to determine zero blood flow. When blood flow ceases, there is no Doppler shift, in which case the received ultrasonic signal is identical to the transmitted signal, indicating zero flow. A square-wave type electromagnetic flowmeter (Benton Instruments) was used to measure renal and iliac blood flows in two fetuses. Further details on the comparison and calibration of these instruments have been published previously (Vatner et al., 1970). One other point deserves mention. Blood flow to the kidney, as measured by the Doppler and electromagnetic techniques, averaged 1.95 ml/min per g in the present study. This value compares favorably with that of Cohn et al. (1974), who used the radioactive microsphere technique, where flow in the kidney averaged 1.75 ml/min per g. Arterial blood gas tensions were measured with a Radiometer acid-base analyzer (PHM 71 Mk 2) and blood microsystem (BMS Mk 2).

On the day of the experiment (1-7 days postoperatively), the ewes were placed in a mobile stall, and measurements of maternal arterial pressure, heart rate, and arterial blood gases and fetal arterial and venous pressures, renal and iliac blood flows, heart rate, and arterial blood gases and intrauterine pressure were obtained for 1-3 hours prior to induction of hypoxemia. Then a mixture of 10% oxygen in nitrogen was administered to the ewe for 10 minutes through a face mask while maternal and fetal hemodynamics were recorded continuously. The responses of animals studied relatively early after operation (1-3 days) and later (4-7 days) were similar. Blood gases were obtained for analysis after 3-5 and 10 minutes of hypoxemia. The mask was then removed and the ewe allowed to breathe room air as hemodynamics were recorded continuously. One to 24 hours after fetal hemodynamics and acid-base balance had returned to the levels obtained prior to hypoxemia, a prostaglandin biosynthesis inhibitor, either sodium meclofenamate (10 mg/kg) or indomethacin (5 mg/kg), was injected intravenously into the fetus over 10 minutes. Twenty minutes after this injection, when fetal hemodynamics had been stable for at least 10 minutes, another 10-minute period of hypoxemia was studied. Maternal and fetal hemodynamics and blood gases were recorded as before. In five ewes the hypoxemia experiment without blockade was repeated, on the same or different days prior to conducting the experiment with prostaglandin synthesis blockade, to ensure that the hemodynamic responses to two 10-minute periods of hypoxemia were reproducible.

Mean pressures and blood flows were obtained by applying their appropriate pulsatile signals to an R-C filter network with a time constant of 2 seconds. Resistance was calculated as the quotient of mean arterial-venous pressure and mean blood flow using a Philbrick divider module. All data were recorded simultaneously and continuously on an eight-channel oscillograph (Brush Instruments, Gould) and on magnetic tape (Bell and Howell) for later playback and analysis. Means and standard errors of the mean were calculated. The significance of the effects of hypoxemia were assessed using the analysis of variance and changes occurring before and after prostaglandin synthesis blockade were compared using the t-test (Snedecor and Cochran, 1967).

Results

The effects of hypoxemia on maternal hemodynamics and arterial blood gases are shown in Table 1. Effects on the fetus are shown in Tables 2-4 and will be described in detail. The hemodynamic data were measured continuously but averaged at 1-3, 5-7, and 10 minutes during the hypoxic stimulus and compared to prehypoxic control values. However, arterial blood gases were only measured at 3-5 and 10 minutes during hypoxemia.

Effects of Hypoxemia in the Fetus

Systemic Effects

At 3-5 minutes after the onset of hypoxemia, fetal PaO₂ fell (P < 0.01) from a control of 20.1 ± 1.4 to 13.4 ± 1.5 mm Hg and was at 8.8 ± 1.0 mm Hg at the end of the hypoxic stimulus (10 minutes). PaCO₂ tended to fall and pH rose slightly during hypoxemia. Arterial blood pH was significantly elevated (P < 0.01) at 10 minutes. Mean arterial pressure increased slightly at 1-3 minutes of hypoxemia from a control of 51 ± 2.0 mm Hg and then rose significantly at 10 minutes. Mean
TABLE 1  Effects of Hypoxemia on Maternal Hemodynamics and Blood Gases in the Presence and Absence of Prostaglandin (PG) Synthesis Blockade

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Early* hypoxemia</th>
<th>Late† hypoxemia</th>
<th>Control</th>
<th>Early* hypoxemia</th>
<th>Late† hypoxemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>82 ± 4.7</td>
<td>95† ± 6.1</td>
<td>95‡ ± 5.1</td>
<td>81 ± 4.9</td>
<td>102‡ ± 4.0</td>
<td>97‡ ± 4.8</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>117 ± 8.3</td>
<td>140‡ ± 6.4</td>
<td>160‡ ± 4.9</td>
<td>118 ± 8.5</td>
<td>135§ ± 7.1</td>
<td>143§ ± 10.8</td>
</tr>
<tr>
<td>Arterial Po₂ (mm Hg)</td>
<td>84.6 ± 4.9</td>
<td>40.1‡ ± 2.0</td>
<td>1.9</td>
<td>82.7 ± 4.5</td>
<td>42.9‡ ± 5.8</td>
<td>36.1‡ ± 3.6</td>
</tr>
<tr>
<td>Arterial PCO₂ (mm Hg)</td>
<td>23.8 ± 4.9</td>
<td>20.4 ± 2.0</td>
<td>2.0</td>
<td>24.1 ± 2.0</td>
<td>20.6 ± 3.6</td>
<td>20.8 ± 3.4</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.46 ± 0.02</td>
<td>7.57‡ ± 0.04</td>
<td>7.58‡ ± 0.03</td>
<td>7.48 ± 0.02</td>
<td>7.54 ± 0.06</td>
<td>7.52 ± 0.02</td>
</tr>
</tbody>
</table>

* Early indicates 1-3 minutes of hypoxemia for hemodynamics and 3-5 minutes for arterial blood gases.
† Late indicates 10 minutes of hypoxemia.
‡ Significant change from control: P < 0.01.
§ Significant change from control: P < 0.05.

Venous pressure did not change significantly from a control of 9.8 ± 3.7 mm Hg. Intrauterine pressures averaged 3.0 mm Hg less than venous pressure and also did not change significantly. Heart rate fell (P < 0.01) at 1-3 minutes of hypoxemia, from a control of 161 ± 6.0 beats/min, and fell further at 10 minutes.

Renal Circulation (n = 11)

The average fetal renal blood flow did not change significantly from 21.1 ± 1.1 ml/min early during hypoxemia, i.e., even up to 7 minutes (Fig. 1). Renal blood flow actually rose in some instances (Fig. 2). However, at 10 minutes of hypoxemia, renal blood flow fell. Renal resistance did not change significantly up to 7 minutes of hypoxemia, but increased at 10 minutes (Table 3). Responses were not different in the five fetal lambs in which the hypoxic stress was repeated either on the same day or on a separate day.

Iliac Circulation (n = 6)

Fetal iliac blood flow (control = 22.4 ± 2.1 ml/min) began to fall shortly after hypoxemia (Fig. 3), decreasing at 1-3 minutes and then further at 5-7 minutes. Iliac resistance rose significantly at 5-7 minutes of hypoxemia (Table 4). Moreover, these changes were significantly different from those observed in the renal circulation (Fig. 4). However, after 10 minutes of hypoxemia, the changes in iliac blood flow and vascular resistance were no longer significantly different from those observed in the

TABLE 2  Effects of Hypoxemia in the Presence and Absence of Prostaglandin (PG) Synthesis Blockade on Fetal Hemodynamics and Blood Gases

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Early* hypoxemia</th>
<th>Late† hypoxemia</th>
<th>Control</th>
<th>Early* hypoxemia</th>
<th>Late† hypoxemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>51 ± 2.0</td>
<td>55 ± 2.5</td>
<td>62‡ ± 3.3</td>
<td>60 ± 2.8</td>
<td>60 ± 3.2</td>
<td>68‡ ± 3.3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>161 ± 6.0</td>
<td>137‡ ± 4.1</td>
<td>122‡ ± 6.2</td>
<td>176 ± 9.0</td>
<td>147‡ ± 7.0</td>
<td>122‡ ± 8.7</td>
</tr>
<tr>
<td>Arterial Po₂ (mm Hg)</td>
<td>20.1 ± 1.4</td>
<td>13.4‡ ± 1.5</td>
<td>8.0‡ ± 1.0</td>
<td>19.3 ± 1.4</td>
<td>13.8‡ ± 1.5</td>
<td>10.8‡ ± 1.7</td>
</tr>
<tr>
<td>Arterial PCO₂ (mm Hg)</td>
<td>34.9 ± 1.9</td>
<td>32.0 ± 3.5</td>
<td>30.8 ± 2.2</td>
<td>35.6 ± 1.7</td>
<td>33.5 ± 3.2</td>
<td>31.0 ± 3.8</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.40 ± 0.01</td>
<td>7.42 ± 0.02</td>
<td>7.45‡ ± 0.01</td>
<td>7.39 ± 0.01</td>
<td>7.40 ± 0.02</td>
<td>7.43 ± 0.03</td>
</tr>
</tbody>
</table>

* Early indicates 1-3 minutes of hypoxemia for hemodynamics and 3-5 min for arterial blood gases.
† Late indicates 10 minutes of hypoxemia.
‡ Significant change from control: P < 0.01.
FIGURE 1 Responses (mean ± SEM) for changes in renal blood flow and renal vascular resistance are plotted for the group of fetal lambs studied in the absence of blockade, shown by the squares, and in the presence of prostaglandin synthesis blockade, shown by the triangles. In the absence of blockade, significant vasoconstriction occurred only at 10 minutes. In contrast, in the presence of prostaglandin synthesis blockade, renal flow began falling immediately, and intense vasoconstriction was noted early. Significantly different responses are denoted between the two conditions.

FIGURE 2 The renal vascular response to a 10-min period of hypoxemia is shown on direct and continuous measurements of phasic and mean arterial pressure, renal blood flow, electronically derived renal vascular resistance, and heart rate in an unanesthetized fetus. The hypoxic stimulus was delivered to the ewe at the time indicated by the arrow. In the normal, unanesthetized fetus, the initial response to hypoxemia does not involve a reduction in renal flow; frequently renal blood flow rose, as occurred in this fetus. Later during the response, renal blood flow fell below control and intense renal vasoconstriction occurred.

Effects of Hypoxemia after Blockade of Prostaglandin Synthesis in the Fetus

In the fetus, the blockade of prostaglandin synthesis with either indomethacin or meclofenamate caused an initial, transient reduction in renal blood flow. However, 30 minutes after blockade, renal blood flow was not significantly different from control, but renal vascular resistance (control = 3.33 ± 0.30 mm Hg/ml per min) was still significantly elevated (P < 0.05). Mean venous and intrauterine pressures rose, but not significantly.

Discussion

The fetal response to hypoxemia is generally thought to involve an increase in arterial pressure and reduction in blood flow to visceral organs, muscle, and skin, while preserving flow to the heart and brain (Assali et al., 1962; Campbell et al., 1967; Cohn et al., 1974). The effect of hypoxemia on fetal heart rate has been controversial. In the present investigation, substantial and reproducible decreases in heart rate with hypoxemia were observed.

Systemic Hemodynamics

The changes in arterial blood gases, mean arterial, venous and intrauterine pressures, and heart rate induced by the hypoxic stimulus were not significantly different after blockade than prior to blockade.

Renal Circulation (n =11)

A typical response to hypoxemia after blockade of prostaglandin synthesis is shown in Figure 5 and can be contrasted with a response prior to blockade in Figure 2. After blockade of prostaglandin synthesis, fetal renal blood flow fell initially at 1–3 minutes after the onset of hypoxemia from a control of 19.1 ± 1.3 ml/min and fell further during the period of hypoxemia (Table 3). These changes were all significant and were significantly different from those prior to blockade of prostaglandin synthesis (Fig. 1). Renal vascular resistance, which, as noted above, was higher after blockade of prostaglandin synthesis, rose significantly during the early response and rose further during the late response. These changes were significantly greater than the changes in resistance observed with hypoxemia prior to blockade (Fig. 1). In two fetuses restudied 1–3 days later without prostaglandin synthesis blockade, hypoxemia failed to induce early renal vasoconstriction, i.e., the renal vascular response to hypoxemia reverted to that observed prior to blockade of prostaglandin synthesis.
Table 3  Effects of Hypoxemia in the Presence and Absence of Prostaglandin (PG) Synthesis Blockade on Fetal Renal Dynamics

<table>
<thead>
<tr>
<th></th>
<th>No blockade</th>
<th>PG blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change from control with hypoxemia at:</td>
<td>Change from control with hypoxemia at:</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>1-3 min</td>
</tr>
<tr>
<td>Mean renal blood flow (ml/min)</td>
<td>21.1 ±1.1</td>
<td>1.41</td>
</tr>
<tr>
<td>Renal vascullar resistance (mm Hg/ml per min)</td>
<td>2.49 ±0.2</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* Significant change from control: \( P < 0.01 \).
† Significant change from control: \( P < 0.02 \).
‡ Responses before and after blockade significantly different: \( P < 0.01 \).
§ Responses before and after blockade significantly different: \( P < 0.05 \).

in all fetuses. This is consistent with the prior work of Assali et al. (1962) and Cohn et al. (1974). Failure to demonstrate a reduction in heart rate in fetal preparations may be due to extreme immaturity of the fetus, where autonomic function is not developed, or to circulatory alterations induced by anesthesia and exteriorization of the fetus (Heymann and Rudolph, 1967).

One of the major findings of the present investigation was that the renal bed responded to hypoxemia differently with time. In contrast to the rapid and marked iliac vasoconstriction which occurred with fetal hypoxemia, the renal bed did not constrict initially and actually dilated in some experiments (Fig. 1). Although these results appear to be inconsistent with those of previous studies, it is important to point out that the present experiments were conducted in unanesthetized fetal lambs in utero as opposed to the majority of previous work (Assali et al., 1962; Campbell et al., 1967). The one previous study on this subject conducted in unanesthetized fetal lambs, that of Cohn et al. (1974), showed a decrease in renal flow with hypoxemia, which was intensified if hypoxemia occurred in combination with acidemia. Since, in the study by Cohn et al. (1974), measurements were made at one point in time (4-44 minutes after initiating the hypoxic stimulus) by the radioactive microsphere technique, it is clear that a biphasic response could not have been observed. Actually, the responses from the renal bed in the group of animals without acidemia were similar to those responses at 10 minutes of hypoxemia in the present investigation, where no acidemia was observed.

In view of the surprising absence of initial renal vasoconstriction with hypoxemia, it was postulated that an opposing vasodilating mechanism, e.g., prostaglandins, was counteracting the sympathetically

![Figure 3](http://circres.ahajournals.org/)

Figure 3  The initial responses to hypoxemia are shown in an unanesthetized fetus, instrumented for direct and continuous measurements of phasic and mean arterial pressure, iliac and renal blood flow, and heart rate. Shortly after the hypoxic stimulus was delivered to the ewe, as indicated by the arrow, the fetus responded with a decrease in heart rate, a slight increase in arterial pressure, and a striking decrease in iliac flow, while renal flow remained essentially constant.
Table 4  Effects of Hypoxemia on Fetal Iliac Dynamics

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>1-3 min</th>
<th>5-7 min</th>
<th>10 min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean iliac blood flow (ml/min)</strong></td>
<td>22.4</td>
<td>-2.4</td>
<td>-8.9*</td>
<td>-8.3*</td>
</tr>
<tr>
<td>± 2.1</td>
<td>± 0.8</td>
<td>± 1.4</td>
<td>± 2.0</td>
<td></td>
</tr>
<tr>
<td><strong>Iliac vascular resistance (mm Hg/ml per min)</strong></td>
<td>2.17</td>
<td>0.30</td>
<td>1.76*</td>
<td>1.71*</td>
</tr>
<tr>
<td>± 0.2</td>
<td>± 0.1</td>
<td>± 0.2</td>
<td>± 0.4</td>
<td></td>
</tr>
</tbody>
</table>

* Significant change from control: P < 0.01.

mediated vasoconstriction. The control of the renal bed by prostaglandins has been well documented in a variety of adult animal species (McGiff et al., 1970; Dunham and Zimmerman, 1970; Herbaczynska-Cedro and Vane, 1973; Lonigro et al., 1973; Vatner, 1974; Swain et al., 1975). In anesthetized animals, inhibitors of prostaglandin synthesis induce a more striking and sustained reduction in renal flow and increase in renal vascular resistance than in conscious animals (Lonigro et al., 1973; Herbaczynska-Cedro and Vane, 1973; Swain et al., 1975). A prior study conducted in our laboratory in conscious dogs indicated that both indomethacin and meclofenamate induced initial transient increases in renal vascular resistance, but meclofenamate caused a more sustained increase in renal vascular resistance. In the present investigation, two prostaglandin synthesis inhibitors which are structurally distinct moieties were used (Flower, 1974). The doses used are recognizable high (indomethacin, 5 mg/kg; meclofenamate, 10 mg/kg) and were given in accordance with an estimated fetal-placental distribution space. The initial injections, made intravenously, uniformly produced transient, intense vasoconstriction. However, steady state hemodynamics 20–40 minutes after injection still showed a modest increase in renal resistance. This suggests a tonic role for prostaglandins in plasma and/or tissue in the regulation of fetal circulation. This role was suggested previously by Challis et al. (1976).

The response of the renal vascular bed in the fetus to hypoxemia was strikingly different after blockade of prostaglandin synthesis. Under these conditions, the renal bed behaved like the iliac, responding promptly with a reduction in blood flow and increase in vascular resistance. The reversal of fetal renal vasodilation during early hypoxemia to marked vasoconstriction after prostaglandin synthesis inhibition is remarkably similar to responses to hemorrhage in conscious dogs (Vatner, 1974). Herbaczynska-Cedro and Vane (1973) provided evidence that intrarenal production, release, and local action of prostaglandins underlie the autoregulation phenomenon in the dog (Owen et al., 1975). Thus, it appears that in the face of hypoxemia, which increases sympathetic tone in the fetus, the kidney responds with an opposing vasodilator mechanism mediated by prostaglandins. After inhibiting the vasodilation mechanism, the full intensity of the sympathetic vasoconstriction can be expressed. A similar phenomenon occurs not only with hemorrhage (Vatner, 1974), but also in response to infusion of peripheral vasoconstrictors (McGiff et al., 1972; Aiken and Vane, 1973; Lonigro et al., 1973; Swain et al., 1975).

It is conceivable that repetitive exposure to hypoxemia results in more intense renal vasoconstriction, and that this, and not prostaglandin synthesis inhibition, was responsible for the different response during the second hypoxic stimulus. Accordingly, repeated exposure to hypoxemia was performed in five ewes without prostaglandin synthesis inhibition. In these experiments, reproducible fetal circulatory responses were observed. Similarly, the reversibility of the renal vasoconstrictor responses after prostaglandin synthesis inhibition was examined by repeating the hypoxic stimulus 1–4 days after treatment. Absence of renal vasoconstriction during the early phase of hypoxemia was again noted by 24 hours after the experiments with pros...
The renal vascular response to hypoxemia after pretreatment with meclofenamate is shown on phasic and mean arterial pressure, renal blood flow, electronically derived renal vascular resistance, and heart rate in an unanesthetized fetal lamb. In contrast to the response in the unblocked fetus in Figure 2, the fetal lamb does not respond with initial renal vasodilation or an increase in renal flow, but in this case, the renal bed responds more like the iliac circulation in that flow rapidly falls and intense vasoconstriction ensues. This vasoconstriction progressively increases during the hypoxic period.

A second possible criticism is that the Doppler flow device, which senses velocity and not volume flow, might indicate an increase in velocity in the renal artery, while volume flow was falling due to constriction of the vessel within the transducer. There are several types of evidence that render this explanation unlikely. First, the responses of renal flow were similar when measured with either the Doppler or electromagnetic flow systems. Second, Doppler flow transducers were used on the iliac artery as well as the renal, and iliac flow fell early during the response to hypoxemia. Third, the renal bed showed vasoconstriction late in the response to hypoxemia in the absence of prostaglandin synthesis blockade and consistently throughout the response to hypoxemia in the presence of prostaglandin synthesis blockade.

It should be noted that the hypoxemia in the fetus was associated with hypocarbia and alkalosis. Thus, all of the renal vascular effects observed in the present study may not be ascribed to hypoxemia alone. However, it is important to note that the changes in fetal arterial P<sub>O2</sub>, P<sub>CO2</sub>, and pH were similar during the early and late periods of hypoxemia, as well as in the presence and absence of prostaglandin synthesis inhibition. Since the renal vascular responses were different during the early and late responses and in the presence and absence of inhibition of prostaglandin synthesis, while the changes in arterial blood gases were similar, it appears that these differences in renal vascular responses were due to a prostaglandin mechanism, rather than to a difference in arterial blood gases. Moreover, it is unlikely that alkalosis and hypocarbia were key factors in the induction of renal vasoconstriction, since Cohn et al., 1974 observed renal vasoconstriction with hypoxemia with both no change in fetal arterial P<sub>CO2</sub>, and pH and, also, in the presence of acidemia.

In conclusion, the fetal peripheral vascular response to hypoxemia involves striking early vasoconstriction in the limb with relative preservation of flow to the renal bed. After blockade of prostaglandin synthesis, the renal bed responded similarly to the iliac, i.e., initial and persistent vasoconstriction was observed with hypoxemia. This suggests that the hypoxic stimulus induced an increase in sympathetic drive to the kidney equivalent to that in the limb, but in the kidney it was attenuated and even reversed in some cases by local prostaglandin mechanisms. Thus, prostaglandins appear to protect the kidney by opposing sympathetic vasoconstriction. These findings may be important clinically, since inhibitors of prostaglandin synthesis are frequently administered to premature infants (Friedman et al., 1976; Heymann et al., 1976), in whom an additional stress such as hypoxemia could intensify renal vasoconstriction in the absence of this important protective mechanism.

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References
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