Effect of maternal undernutrition in early gestation on ovine fetal blood pressure and cardiovascular reflexes

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Received 8 June 1999; accepted in final form 27 January 2000

Hawkins, Paul, Clare Steyn, Takashi Ozaki, Tsukuru Saito, David E. Noakes, and Mark A. Hanson. Effect of maternal undernutrition in early gestation on ovine fetal blood pressure and cardiovascular reflexes. Am J Physiol Regulatory Integrative Comp Physiol 279: R340–R348, 2000.—Human epidemiological and animal experimental studies suggest that maternal undernutrition during pregnancy may alter cardiovascular development of the offspring. The extent to which these effects involve changes in fetal cardiovascular function and whether they are necessarily linked to reduced fetal growth is unknown. In sheep, we investigated the effect of a 15% reduction in maternal global nutrition for the first 70 days of gestation (term = 147 days) on fetal blood pressure development, baroreflex control of fetal heart rate (FHR), and cardiovascular responses to acute hypoxemia in late gestation. Basal mean arterial pressure (P < 0.05), systolic blood pressure (P < 0.05), diastolic blood pressure (P < 0.05), and rate-pressure product (P < 0.001) were significantly lower in fetuses of nutritionally restricted ewes (R) compared with controls (C). FHR was not altered. The operating point for the fetal baroreflex was significantly lower in R fetuses compared with C (P < 0.01), but there was no difference between the groups in the cardiovascular response to hypoxemia. We conclude that mild maternal undernutrition alters fetal cardiovascular development, producing low blood pressure and resetting of baroreflex control mechanisms. This effect occurs without any changes in fetal growth or blood gas status.

fetal sheep; baroreflex; chemoreflex; programming

Recent epidemiological observations have linked reduced fetal growth with increased risk of cardiovascular disease in adult life (3). Maternal undernutrition is one factor that may alter fetal growth and development of fetal organ systems (“programming” of development), including the cardiovascular system. Studies in rats have demonstrated an important effect of maternal undernutrition, with either protein (15) or global (18, 26) dietary restriction producing offspring with elevated blood pressure. The mechanisms by which this effect is produced may be initiated in fetal life. However, the effects of maternal nutrient restriction on fetal cardiovascular development are at present unknown.

There are now several lines of evidence that suggest that reduction of fetal growth or birth weight is not a necessary prerequisite for the development of perturbed cardiovascular and endocrine function in the adult (see Ref. 9 for review). If the maternal dietary impairment is not severe, fetal and placental compensatory mechanisms may be adequate, and birthweight may not be reduced. However, the programming of fetal cardiovascular development may be altered as the cardiovascular system forms a key component of the fetal compensation, and such altered programming may persist postnatally. The aim of our experiments was thus to examine the effects of mild maternal undernutrition in early gestation on fetal arterial blood pressure over a period of 2 wk in late gestation. In addition, because the fetal cardiovascular system is regulated by baro- and chemoreflexes in late gestation (2, 6), we measured fetal heart rate (FHR) responses to changes in blood pressure and chemoreflex responses to hypoxemia to determine whether any changes in blood pressure were accompanied by alterations in these reflexes.

METHODS

Dietary Manipulation

Before conception, parous Welsh Mountain ewes of uniform age, weight, and body condition score were randomly assigned to either the control (C) or the nutrient-restricted (R) group. Ewes were housed in individual pens with wood shavings for bedding and fed a complete pelleted diet according to body weight, condition score, and stage of gestation. Animals were allowed free access to water. The diet consisted of barley, wheat, cooked cereal meal, micronized full fat soya, grass meal, molasses, chopped straw, calcium carbonate, dicalcium phosphate, salt, and a sheep vitamin/mineral supplement. It provided 10.81 MJ/kg metabolizable energy and 149.8 g/kg crude protein and contained 88.4% dry matter. Feeding was based on recommendations made by an advisory manual prepared by the Agricultural and Food Research

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Council Technical Committee on responses to nutrients (1). Nutrient intake was modified by reducing the amount of the recommended daily ration in this study so that all components of the diet were reduced by the same degree.

C animals were fed 100% of their recommended nutritional requirements for the whole of gestation (term = 147 days). R animals received 85% of their recommended nutrient requirements from the time of conception until day 70 of gestation and 100% of their requirements thereafter. Thus R animals received 15% less compared with C for the first 70 days of gestation only. Maternal body weight and condition score (21) were measured on a weekly basis.

Surgical Procedures

All surgical procedures were approved by the Home Office and were conducted in accordance with the Animals (Scientific Procedures) Act, 1986. Aseptic surgery was performed on 13 singleton-bearing ewes at 106–109 days gestation (dGA) and on two singleton-bearing ewes at 118 and 124 dGA under general anesthesia (thiopentone, 1 g iv for induction; 2% halothane in O₂ for maintenance). The uterus was exposed through an incision in the midline of the lower abdominal wall, and the fetus was partially exteriorized. Catheters filled with heparinized saline (50 IU/ml) were placed in a fetal carotid artery and a jugular vein, and a nonheparinized catheter was placed in the amniotic cavity. Stainless steel electrodes were sewn subcutaneously onto the chest and head to record electrocardiogram (ECG). A catheter was also placed in a maternal pedal vein. Incisions were closed and the fetal catheters and electrode cable were exteriorized through a small puncture in the maternal abdominal wall. At least 4 days postoperative recovery were allowed before commencing experiments. During this time, antibiotics were administered daily to the ewe (Crystapen, 300 mg iv), fetus (Crystapen, 150 mg iv), and amniotic cavity (Crystapen, 150 mg iv). Gentamicin was administered on days 1 and 2 only to the ewe (40 mg iv) and amniotic cavity (40 mg). Catheters were maintained patent by continuous infusion of heparinized saline (50 IU/ml at 0.125 ml/h). Fetal arterial blood (0.5 ml) was collected daily for pH, blood gas, hematocrit (Hct), Hb, and blood glucose and lactate analysis.

Experimental Procedures

Basal recordings. Fetuses were studied over a 13-day period between 114–115 and 126–130 dGA. In most animals, seven recordings (2 h) of basal cardiovascular variables were made during the course of the study. These were made in the morning on alternate days. Fetal arterial blood (0.5 ml) was collected daily for pH, blood gas, hematocrit (Hct), Hb, and blood glucose and lactate analysis.

Baroreflex. Fetal baroreflexes were examined at 114–115, 120–123, and 126–130 dGA by administering an intravenous bolus of phenylephrine (75 µg). Phenylephrine was dissolved in sterile saline (0.9%) and administered in a volume of 1 ml. Continuous recordings of fetal arterial pressure and ECG from 3 min before until 10 min after injection of the drug. R-R interval was used as the baseline for each heart beat. Baroreflex curves were generated from data between baseline SBP and the maximum SBP after phenylephrine administration.

Chemoreflex. Fetal responses to acute isocapnic hypoxemia were also examined at 114–115, 120–123, and 126–130 dGA. A transparent bag was placed over the ewe’s head, into which known concentrations of O₂, N₂, and CO₂ were passed at −44 l/min. After a 1-h normoxic control period of breathing air, fetal hypoxemia (PaO₂ reduced from −25 to −13 mmHg) was induced for a further 60 min by reducing maternal FIO₂ (14 l/min air, 22 l/min N₂, 1.2 l/min CO₂). At the end of the hypoxemia period, fetuses were returned to normoxic conditions (recovery period) for an additional hour. Samples of fetal arterial blood (0.5 ml) were collected 30 min before and 15 and 45 min after the start of hypoxemia and 30 min after the start of the recovery period (+30 min) for blood gas analysis.

Recording methods. Basal cardiovascular variables, and responses to hypoxemia and phenylephrine were monitored by making continuous recordings of arterial pressure, venous pressure, FHR, and ECG during each experiment using MacLab/8 hardware and data-acquisition software. Fetal blood pressures were corrected for amniotic pressure by subtraction of the amniotic pressure from blood pressure. Mean arterial pressure (MAP), SBP, diastolic blood pressure (DBP), and rate-pressure product (RPP) were determined. For the basal and hypoxemia experiments, mean values of cardiovascular variables were obtained by averaging data over 1-min periods at 15-min intervals throughout the experiment. Additional mean values were also calculated at 5 and 10 min after the start of hypoxemia.

At the end of the study period at 127–131 dGA, ewes were killed by an overdose of pentobarbitone (Euthatal 40 ml iv; Rhône Mérieux, Harlow, Essex, UK). Maternal and fetal body weight, fetal heart, lung, liver, individual kidney, and individual adrenal weight, crown-rump length, abdominal circumference, and femur length were recorded. The fetal body and organs were examined for any macroscopic abnormalities.

Blood Gas Analysis

Blood gases, pH, and Hct were measured on a blood gas analyzer (BGE, Instrumentation Laboratory, values corrected to 39.5°C). A hemoximeter was used for measurement of Hb (CO-oximeter 482, Instrumentation Laboratory, Warrington, Cheshire, UK), and glucose and lactate were measured by glucose-lactate analyzer (YSI, 2300 STAT PLUS).

Data Analysis

All values are presented as means ± SE. When multiple comparisons were made, P values were corrected using the Bonferroni method. Data were compared between C and R fetuses using summary measures analysis (16) and analysis of variance. Significance was accepted when P < 0.05.

Organ weight data. Data for fetal body proportions, body-weight, and organ weights were compared between C and R fetuses using Student’s unpaired t-test.

Blood gas data. Values for basal blood gas parameters were calculated by averaging the data collected over the course of the study period in each animal. These values were then averaged to produce an overall mean for the group. Data were compared between C and R fetuses using Student’s unpaired t-test. Differences in blood gas data between C and R fetuses during the hypoxemia experiments were determined by comparing each data point using Student’s unpaired t-test. The change in blood gas parameters during hypoxemia within each group were analyzed by comparing the normoxic value at −30 min with the subsequent values under hypoxicemic and recovery conditions. Significance was determined using Student’s paired t-test.

Cardiovascular data. Basal cardiovascular data were compared between C and R fetuses by two-way analysis of variance, comparing the effect of group (C vs. R), age, and the interaction between group and age. If a significant effect of age was found, post hoc analysis using Student’s paired t-test.
was performed to compare the first and last values within each group.

Baroreflex responses were analyzed on a beat-to-beat basis. For each SBP peak, the corresponding interval between the R waves of the ECG (R-R interval) was calculated. This was performed from the period of baseline arterial pressure before the drug injection until the maximum arterial pressure had been reached. Baroreflex curves were then plotted for SBP against R-R interval, and the slope of the steepest portion of each curve was measured. In addition, an operating point was determined for each baroreflex as follows. First, maximum and minimum R-R intervals were calculated for each response by averaging the three highest and the three lowest R-R intervals, respectively. These values were designated as 0% and 100% of the response. Intermediate values were converted into proportional percentages, and SBP was then plotted against the R-R interval as a percentage of the maximum (Fig. 1). The operating point was determined as the SBP that produced 50% of the response. Baroreflex data were compared between C and R fetuses by two-way analysis of variance, comparing the effect of group (C vs. R), age, and the interaction between group and age. Values were determined as the SBP that produced 50% of the response. Baroreflex curves were then plotted for SBP against R-R interval, and the slope of the steepest portion of each curve was measured. In addition, an operating point was determined for each baroreflex as follows. First, maximum and minimum R-R intervals were calculated for each response by averaging the three highest and the three lowest R-R intervals, respectively. These values were designated as 0% and 100% of the response. Intermediate values were converted into proportional percentages, and SBP was then plotted against the R-R interval as a percentage of the maximum (Fig. 1). The operating point was determined as the SBP that produced 50% of the response. Baroreflex data were compared between C and R fetuses by two-way analysis of variance, comparing the effect of group (C vs. R), age, and the interaction between group and age. Values were compared between gestational ages within each group by Student's paired t-test.

During the hypoxemia experiments, cardiovascular data were grouped (i.e., averaged) at four time periods. These were 1) normoxia (whole of normoxic hour), 2) early hypoxemia (value at 5 min of hypoxemia), 3) late hypoxemia (last 30 min of hypoxemia), and 4) recovery (last 30 min of recovery). Data were compared between C and R fetuses at each of these time points using Student’s unpaired t-test. Changes in cardiovascular variables within each group were determined by comparing the normoxia value with each of the three subsequent values, i.e., early + late hypoxemia and recovery. Significance was determined by Student’s paired t-test.

**Comments.** This study was conducted on a total of 15 Welsh Mountain breed sheep [C (n = 7), R (n = 8)]. During the course of the study, two of the R ewes chewed and destroyed the fetal catheters. These animals were then removed from further experiments, one after 115 dGA and one after 123 dGA. They were replaced by two R animals at these ages, so that the total number studied for each hypoxemia or baroreflex experiment remained at n = 7 for C and n = 6 for R.

**RESULTS**

**Maternal Body Weight and Condition Score**

Maternal data have been reported previously in a larger group of animals of which the present group were a subset (8). Briefly, when expressed as a percent change from values at mating, there was a significant difference between C and R ewes for body weight at 0–70 dGA and for condition score at 0–70, 70–119, and 0–119 dGA.

**Fetal Growth and Organ Weights**

There were no significant differences between C and R fetuses for any of the measurements of fetal growth or fetal organ weights (Table 1).

**Blood Gases**

Mean basal blood gas parameters did not differ between C and R fetuses (Table 2). There were no differences between C and R fetuses for any parameter of blood gas status during the hypoxemia experiments (e.g., Table 3; for further data, see tables in APPENDIX).
Typically, pH was significantly lower during hypoxemia compared with normoxia in both groups of fetuses. $P_{aCO_2}$ did not change significantly in either C or R fetuses during hypoxemia. $P_{aO_2}$ and Hb were significantly lower during both early and late hypoxemia compared with normoxia in C and R fetuses at all ages. Hypoxemia caused a significant increase in lactate compared with normoxic conditions in both C and R fetuses. Glucose also increased significantly during hypoxemia, although not consistently.

### Basal Cardiovascular Development

Basal blood pressure was significantly lower in R fetuses compared with C fetuses in terms of MAP ($P < 0.05$), SBP ($P < 0.05$), and DBP ($P < 0.05$; Fig. 2). FHR was not different between C and R fetuses. RRP ($P < 0.001$) was significantly lower in R fetuses compared with C fetuses. MAP did not change significantly in C fetuses between 114 and 126 dGA. In R fetuses, MAP was greater at 126 dGA compared with 114 dGA ($P < 0.05$). SBP increased significantly in both C ($P < 0.05$) and R ($P < 0.02$) fetuses when 114 dGA was compared with 126 dGA. DBP was greater at 126 dGA compared with 114 dGA in C fetuses ($P < 0.01$), but in R fetuses, no significant change was observed. RPP was similar at 114 and 126 dGA in both C and R fetuses. FHR decreased significantly between 114 and 126 dGA in both C ($P < 0.01$) and R ($P < 0.05$) fetuses.

### Baroreflex Responses

The operating point of the baroreflex was significantly lower in R fetuses compared with C fetuses ($P < 0.01$; Table 4). In C fetuses, the operating point was significantly greater at 120–123 dGA compared with 114–115 dGA ($P < 0.05$). There were no other differences in operating point between gestational ages in C or R fetuses. The slope of the baroreflex was not different between C and R fetuses. In addition, it did not differ between gestational ages for either group of fetuses.

### Cardiovascular Response to Hypoxemia

There were no differences in the cardiovascular response to hypoxemia between C and R fetuses at any of the ages studied (Figs. 3-5). Broadly, the changes were as expected from previous studies. FHR fell significantly in early hypoxemia, and in the recovery period, it increased significantly above normoxic values. MAP, SBP, and DBP were greater in late hypoxemia compared with normoxia and returned to normoxic values during recovery. The changes in blood pressure were not always consistent, as reported by others.

### Discussion

The results of this study show that mild maternal undernutrition in early gestation alters fetal cardiovascular development, producing changes that are manifest in late gestation. The most important observation is that fetuses of nutritionally restricted ewes have low basal blood pressure in terms of MAP, SBP, and DBP. RPP is also lower in this group, suggesting that cardiac output is reduced. Basal heart rate was not significantly altered by the nutritional challenge. The cardiovascular response to hypoxemia was similar in both groups of fetuses, indicating that chemoreflex control mechanisms were operating correctly, at least in terms of the control of blood pressure and heart rate. The baroreflex function curve was shifted to the left in fetuses of nutritionally restricted ewes, demonstrating that the operating range of blood pressures for this
reflex was reduced. This finding emphasizes that the resetting of blood pressure regulation to a lower level in R fetuses was a long-term phenomenon. These changes occurred despite there being no differences in fetal blood gas status or growth between R and C fetuses.

Perturbation of Basal Cardiovascular Development

The finding that blood pressure increased and FHR fell in both C and R fetuses in the present study suggests that normal developmental processes are occurring in both groups (4, 13, 20). Thus the lower blood pressure in R fetuses could indicate that this group was “immature” in terms of blood pressure development. One possibility is that if R fetuses had been smaller compared with C fetuses, the structural determinants of blood pressure development, such as heart size and growth of the vasculature, may also have been at a less-advanced stage. However, as fetal body and organ weights were not different between C and R fetuses, this possibility appears unlikely. In addition, development of FHR was not different between the groups.

In basic terms, fetal blood pressure is determined by combined ventricular output (CVO) and vascular resistance. Therefore, alterations in one or both of these parameters must have occurred in R fetuses to produce the reduction of MAP. The results of this study show that RPP was significantly reduced in R fetuses. RPP has been used as an index of cardiac work (11, 12, 17); hence, CVO may have been reduced in this group, resulting in the low MAP. In the present study it was shown that FHR was not different between the two groups of fetuses. Therefore, if CVO was reduced in R fetuses, it was almost certainly due to a reduction in stroke volume. We did not observe an overall difference in heart weight between R and C fetuses but did not measure cardiac chamber size or wall thicknesses. The possible effects of mild maternal undernutrition on growth of the fetal heart merit further investigation.

A decrease in peripheral vascular resistance could have produced the low blood pressure in R fetuses. This could occur by a reduction in efficacy of endogenous vasoconstrictors or increase in efficacy of vasodilators. These effects may involve alterations in receptor numbers, changes in signal transduction.

Table 4. Data for the operating point and slope of the baroreflex curves at 114–115, 120–123, and 126–130 dGA in C and R fetuses

<table>
<thead>
<tr>
<th>Gestational Age, days</th>
<th>114–115</th>
<th>120–123</th>
<th>126–130</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operating point, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>65.2 ± 1.2</td>
<td>71.9 ± 1.3a</td>
<td>74.6 ± 4.2</td>
</tr>
<tr>
<td>(n = 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>60.8 ± 1.3</td>
<td>64.3 ± 1.2</td>
<td>65.5 ± 1.8</td>
</tr>
<tr>
<td>(n = 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope, ΔSBP/ΔR-R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0.017 ± 0.007</td>
<td>0.012 ± 0.002</td>
<td>0.017 ± 0.004</td>
</tr>
<tr>
<td>R</td>
<td>0.018 ± 0.005</td>
<td>0.014 ± 0.005</td>
<td>0.025 ± 0.015</td>
</tr>
</tbody>
</table>

Values are presented as means ± SE. *P < 0.05 (paired t-test) compared with value at 114 dGA. Note that the operating point of the baroreflex was significantly lower in R fetuses compared with C fetuses (P < 0.01; ANOVA). There were no differences in slope between C and R fetuses. For C, n = 7, and R, n = 6, unless stated. SBP, systolic blood pressure; Δ, change.

Fig. 2. Basal cardiovascular variables in control (C, n = 7) and restricted (R, n = 6) fetuses. Values are shown as means ± SE. MAP, mean arterial pressure; DBP, diastolic blood pressure; RPP, rate-pressure product; FHR, fetal heart rate; bpm, beats/min.
mechanisms, or changes in the circulating concentrations of vasoactive agents. In companion studies, we have demonstrated that activity of the fetal hypothalamic-pituitary-adrenal (HPA) axis is reduced in fetuses of nutritionally restricted ewes (8). As glucocorticoids are known to produce an increase in fetal MAP (25), reduced HPA axis activity could contribute to a reduction of vascular tone and MAP. It will be important to examine further the effects of maternal undernutrition on function of the fetal HPA axis and also on the other endocrine components of fetal cardiovascular regulation.

Structural changes in the fetal circulation could also produce a decrease in vascular resistance. The major determinant of peripheral resistance in the fetus is the umbilical-placental circulation (10), and in separate studies, we showed that maternal undernutrition can produce an increase in the proportion of the type D placentomes (5) and an elevation of fetal placental villous density (14). These changes are characteristic of an increase in size of the fetal side of the placenta, and, if accompanied by an increase in vascularity, could lead to a reduction of placental vascular resistance and a decrease in fetal MAP. We are currently investigating the effects of maternal undernutrition on markers of placental vascular growth.

Baroreflex Responses

The results show that the operating point of the baroreflex was significantly lower in R fetuses com-

![Fig. 3. Cardiovascular variables in C and R fetuses during hypoxemia at 114–115 dGA. The shaded bar indicates the period of hypoxemia (60 min). Values are means ± SE. Note that there were no differences between C and R fetuses.](image)

![Fig. 4. Cardiovascular variables in C and R fetuses during hypoxemia at 120–123 dGA. The shaded bar indicates the period of hypoxemia (60 min). Values are means ± SE. Note that there were no differences between C and R fetuses.](image)
pared with C fetuses. However, the gain of the reflex, as indicated by the slope of the curve, did not differ between the two groups of fetuses at any of the ages studied. The operating point of the baroreflex function curve shifts to the right as blood pressure increases during development (2, 22, 23). As the operating point of the reflex was lower in R fetuses, it is clear that their low MAP was a chronic condition and not a transient effect. We would predict that a lower MAP would also be associated with a greater baroreflex gain; however, our results indicate that this was not the case. This observation could be important as it suggests that this component of the baroreflex was set to regulate arterial pressure at its normal level for gestation and not the lower pressure level that was found.

Responses to Hypoxemia

There did not appear to be any effect on the cardiovascular response to hypoxemia after maternal undernutrition, suggesting that chemoreflex control of the fetal circulation was not altered, at least in terms of blood pressure and FHR control. More severe nutritional challenges, such as those produced by restriction of placental size, have demonstrated alterations in the cardiovascular response to acute hypoxemia (19), which are thought to be due to increased activity of the sympathetic nervous system (24). Restriction of placental size is often accompanied by chronic fetal hypoxemia and therefore might be expected to produce changes in chemoreflex function. The absence of any effects on fetal blood gas status in the present study may explain the apparent lack of a change in chemoreflex function. Blood pressure during the hour of normoxia tended to be lower in R fetuses compared with C fetuses, particularly at 114–115 and 126–130 dGA, which is consistent with the results of the study of basal cardiovascular development. However, this did not reach significance. The reason for this difference between the two studies is not clear but may relate to the fact that during the hypoxemia experiment, disturbances to fetal blood pressure may have been produced by the different experimental conditions.

Summary

These studies support the hypothesis that maternal undernutrition alters development of the fetal cardiovascular system, even at a level that does not affect fetal growth or blood gas status. Fetuses of ewes that were nutritionally restricted have lower blood pressures and reduced RPP. The chronic nature of these effects is reinforced by the finding of resetting of baroreflex control mechanisms. The data suggest that reduction of CVO or decreased placental vascular resistance could be involved in mediating the decrease in blood pressure. In addition, the changes in cardiovascular development may be linked to altered development of the HPA axis (8).

This study does not appear, initially, to support the findings of other studies of maternal undernutrition that have produced hypertension when studied postnatally. If the changes in cardiovascular development described in the present study are part of the mechanism by which blood pressure becomes elevated in postnatal life, then clearly, a transition must occur at some stage. Indeed, this is exactly what we find, as blood pressure is elevated postnatally in R lambs (7). Thus it is possible that development of postnatal hypertension may be initiated in utero, although the mechanisms involved produce low blood pressure in fetal life. These findings are striking in the context of epidemiological studies that have linked early life events with increased risk of adult disease (3). Thus it will be particularly important to examine the mechanisms that underlie these changes in fetal cardiovas-

Fig. 5. Cardiovascular variables in C and R fetuses during hypoxemia at 126–130 dGA. The shaded bar indicates the period of hypoxemia (60 min). Values are means ± SE. Note that there were no differences between C and R fetuses.
cular development and to investigate the implications for organ function in the adult.

**Perspectives**

This study provides further evidence for effects of maternal diet in early gestation on the programming of cardiovascular development. Clearly, fetal growth does not have to be reduced for such effects to be seen; so the biological mechanisms are not solely associated with intrauterine growth retardation. Our findings are interesting because we find a lower blood pressure in late-gestation fetuses of dietary-restricted ewes. Other studies show that a transition to elevated blood pressure occurs postnatally; so the processes involved in this transition need to be investigated. The sheep model will provide valuable insights into the mechanisms of these effects and their possible pathological significance in the human.

**APPENDIX**

**Table A1. Blood gas parameters during hypoxemia at 120–123 dGA in C and R fetuses**

<table>
<thead>
<tr>
<th></th>
<th>Normoxia</th>
<th>Hypoxemia</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>~30 min</td>
<td>15 min</td>
<td>45 min</td>
</tr>
<tr>
<td>pH C</td>
<td>7.33 ± 0.01</td>
<td>7.30 ± 0.02*</td>
<td>7.25 ± 0.02†</td>
</tr>
<tr>
<td>R</td>
<td>7.34 ± 0.00</td>
<td>7.31 ± 0.01*</td>
<td>7.26 ± 0.01†</td>
</tr>
<tr>
<td>PaCO₂, mmHg C (n = 6)</td>
<td>44.1 ± 1.1</td>
<td>46.1 ± 1.0</td>
<td>42.6 ± 1.6</td>
</tr>
<tr>
<td>R</td>
<td>40.4 ± 2.1</td>
<td>41.1 ± 2.4</td>
<td>41.3 ± 1.9</td>
</tr>
<tr>
<td>PaO₂, mmHg C</td>
<td>26.9 ± 0.5</td>
<td>13.0 ± 0.4†</td>
<td>14.6 ± 0.5§</td>
</tr>
<tr>
<td>R</td>
<td>26.5 ± 1.7</td>
<td>15.2 ± 0.6†</td>
<td>15.0 ± 0.9†</td>
</tr>
<tr>
<td>Hct, % C</td>
<td>25.4 ± 1.7</td>
<td>28.3 ± 1.6†</td>
<td>25.9 ± 1.6</td>
</tr>
<tr>
<td>R</td>
<td>22.2 ± 1.2</td>
<td>25.7 ± 1.2‡</td>
<td>25.5 ± 1.5§</td>
</tr>
<tr>
<td>Hb g/dl C</td>
<td>7.5 ± 0.6</td>
<td>6.0 ± 0.4†</td>
<td>5.8 ± 0.4†</td>
</tr>
<tr>
<td>R</td>
<td>7.1 ± 0.5</td>
<td>5.9 ± 0.3*</td>
<td>5.6 ± 0.3*</td>
</tr>
<tr>
<td>Lactate (mM) C</td>
<td>0.79 ± 0.05</td>
<td>2.31 ± 0.26†</td>
<td>4.31 ± 0.45§</td>
</tr>
<tr>
<td>R</td>
<td>0.83 ± 0.10</td>
<td>1.99 ± 0.33*</td>
<td>3.88 ± 0.40§</td>
</tr>
<tr>
<td>Glucose (mM) C</td>
<td>0.82 ± 0.02</td>
<td>0.97 ± 0.07</td>
<td>0.99 ± 0.08</td>
</tr>
<tr>
<td>R</td>
<td>0.78 ± 0.04</td>
<td>0.99 ± 0.04*</td>
<td>1.09 ± 0.09*</td>
</tr>
</tbody>
</table>

Values are presented as means ± SE. *P < 0.05, †P < 0.01, ‡P < 0.001, §P < 0.0001 (paired t-test) compared with value at ~30 min. For C, n = 7, and R, n = 6, unless stated.

**Table A2. Blood gas parameters during hypoxemia at 126–130 dGA in C and R fetuses**

<table>
<thead>
<tr>
<th></th>
<th>Normoxia</th>
<th>Hypoxemia</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>~30 min</td>
<td>15 min</td>
<td>45 min</td>
</tr>
<tr>
<td>pH C</td>
<td>7.33 ± 0.01</td>
<td>7.31 ± 0.01</td>
<td>7.22 ± 0.03†</td>
</tr>
<tr>
<td>R</td>
<td>7.34 ± 0.01</td>
<td>7.33 ± 0.01</td>
<td>7.28 ± 0.01*</td>
</tr>
<tr>
<td>PaCO₂, mmHg C (n = 5)</td>
<td>44.4 ± 1.6</td>
<td>43.2 ± 1.6</td>
<td>45.9 ± 2.0</td>
</tr>
<tr>
<td>R</td>
<td>42.5 ± 2.4</td>
<td>41.8 ± 2.3</td>
<td>45.8 ± 1.2</td>
</tr>
<tr>
<td>PaO₂, mmHg C</td>
<td>25.6 ± 0.9</td>
<td>13.9 ± 0.6§</td>
<td>14.4 ± 0.9§</td>
</tr>
<tr>
<td>R</td>
<td>28.7 ± 0.8</td>
<td>13.7 ± 0.4‡</td>
<td>14.2 ± 0.2‡</td>
</tr>
<tr>
<td>Hct, % C</td>
<td>25.9 ± 1.9</td>
<td>27.7 ± 1.5</td>
<td>29.4 ± 1.9§</td>
</tr>
<tr>
<td>R</td>
<td>21.5 ± 1.5</td>
<td>23.7 ± 1.9*</td>
<td>25.3 ± 1.7*</td>
</tr>
<tr>
<td>Hb g/dl C</td>
<td>7.5 ± 0.6</td>
<td>6.2 ± 0.5*</td>
<td>6.2 ± 0.4†</td>
</tr>
<tr>
<td>R</td>
<td>7.1 ± 0.3</td>
<td>5.8 ± 0.2‡</td>
<td>5.9 ± 0.2‡</td>
</tr>
<tr>
<td>Lactate, mM C</td>
<td>0.88 ± 0.09</td>
<td>2.12 ± 0.24†</td>
<td>4.79 ± 0.53‡</td>
</tr>
<tr>
<td>R</td>
<td>0.88 ± 0.06</td>
<td>1.95 ± 0.11†</td>
<td>4.36 ± 0.29‡</td>
</tr>
<tr>
<td>Glucose, mM C</td>
<td>0.82 ± 0.06</td>
<td>1.01 ± 0.12</td>
<td>1.17 ± 0.10†</td>
</tr>
<tr>
<td>R</td>
<td>0.76 ± 0.04</td>
<td>0.85 ± 0.03</td>
<td>0.99 ± 0.03*</td>
</tr>
</tbody>
</table>

Values are presented as means ± SE. *P < 0.05, †P < 0.01, ‡P < 0.001, §P < 0.0001 (paired t-test) compared with value at ~30 min. For C, n = 7, and R, n = 6, unless stated.
We are grateful to the Wellcome Trust and British Heart Foundation for financial support.
P. H. was an Medical Research Council postgraduate student.

REFERENCES


