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Cardiovascular Responses to Hypoxemia in Sinoaortic-Denervated Fetal Sheep

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ABSTRACT. Fetal cardiovascular response to acute hypoxemia is characterized by bradycardia, hypertension, and redistribution of cardiac output. The role of aortic and carotid chemoreceptors in mediating these responses was examined in eight sinoaortic-denervated and nine sham-operated fetal lambs. Blood gases, pH, heart rate, arterial pressure, and blood flow distribution were determined before and during hypoxemia. In intact fetuses, heart rate fell from 184 ± 12 to 165 ± 23 beats/min ($p < 0.01$) but increased from 184 ± 22 to 200 ± 16 beats/min ($p < 0.05$) in the sinoaortic-denervated fetuses. Intact fetuses showed an early hypertensive response to hypoxemia, whereas the sinoaortic-denervated fetuses developed a delayed, progressive rise in blood pressure. In both groups, fetal cardiac output and umbilical blood flow were maintained; cerebral, myocardial, and adrenal blood flow increased, and pulmonary blood flow decreased. Peripheral blood flow decreased 39% ($p < 0.001$) in intact fetuses but was maintained in sinoaortic-denervated fetuses. Vascular responses to hypoxia in the brain, heart, adrenal, and lungs are regulated primarily by direct local effects. During hypoxemia, peripheral chemoreceptors mediate bradycardia and peripheral vasoconstriction but do not appear to be crucial for immediate fetal survival. (*Pediatr Res* 30: 381–385, 1991)

Abbreviations

SAD, sinoaortic denervation

Fetal cardiovascular responses to acute hypoxemia include bradycardia, peripheral vasoconstriction and hypertension, and redistribution of cardiac output to favor the brain and heart at the expense of the peripheral and pulmonary circulations (1). Several neurohormonal mechanisms have been shown to be involved in mediating these circulatory responses. Activation of the sympathetic nervous system through its peripheral nerve terminals mediates the vasoconstrictor response in the peripheral, gastrointestinal, and renal vascular beds (2–4), whereas increased vagal tone results in slowing of fetal heart rate (5–8). Acute hypoxemia also stimulates the release of catecholamines (9, 10), vasopressin (11), and renin (12), which, through their interaction with the cardiovascular or nervous system, participate in the circulatory responses to hypoxemia.

The peripheral arterial chemoreceptors situated in the carotid and aortic bodies are of major importance in the reflex control of respiratory, cardiovascular, and endocrine responses to acute hypoxemia in postnatal life (13). The vascular effects of peripheral chemoreceptor stimulation, with ventilation held constant, include coronary vasodilation and vasoconstriction in the splanchnic organs and the skeletal muscles. Stimulation of the carotid body chemoreceptors results in reflex bradycardia and negative inotropic responses. The bradycardia and peripheral vasoconstriction during carotid chemoreceptor stimulation can be reversed by effects arising from concurrent hypernea (13).

The arterial chemoreceptors (aortic and carotid bodies) are active in the fetal lamb and are responsive to hypoxemia (14–21). Stimulation of the fetal arterial chemoreceptors result in bradycardia, which is abolished by SAD (19, 20, 22). However, the role of these chemoreceptors in mediating the integrated response of the fetal circulation to acute hypoxemia is not known. The study presented here was designed to investigate the relative importance of the aortic and carotid receptors in determining the fetal cardiovascular responses to hypoxemia. Hypoxemia was produced in conscious ewes, and the cardiovascular responses to hypoxemia in intact fetuses were compared with the responses observed in a group of SAD fetuses.

MATERIALS AND METHODS

Animal preparation. We studied fetal lambs at 120 to 128 d of gestation (term, ~147 d) at the time of surgery. The study protocol was approved by the Committee on Animal Research at the University of California San Francisco.

After 24 to 48 h of fasting, the ewe received spinal anesthesia (2 mL of 1% tetracaine hydrochloride); sedation was achieved with i.v. injections of 60 mg of pentobarbital sodium every 10 to 15 min, or more frequently if necessary. Under aseptic conditions, polyvinyl catheters were inserted into the maternal pedal artery and vein and advanced to the descending aorta and inferior vena cava. The uterus was exposed through a midline abdominal incision, and the fetal parts were identified.

SAD was performed on eight fetuses as previously reported (19). Briefly, the head was exposed through a uterine incision. Through incisions just below the angle of the jaw on each side, the carotid artery and vagus nerve were identified. Carotid body denervation was accomplished by vascular stripping of the carotid artery and cutting the carotid sinus nerve. Aortic denervation was accomplished by cutting the superior laryngeal nerves at their origin from the vagal nerves. It has been shown that the aortic nerve ascends in the angle between the vagus and superior laryngeal nerves.

Polyvinyl catheters were inserted bilaterally into the carotid artery through the lingual artery and into the superior vena cava through a branch of the external jugular vein. The trachea was also cannulated (20, 23). Through a second uterine incision, the pedal vein and artery were catheterized bilaterally and the tips of the catheters were advanced to the distal inferior vena cava and descending aorta. A catheter was also placed in the amniotic cavity. The vascular catheters were passed to the flank of the ewe, where they were protected by a pouch sewn to the skin.

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Nine fetuses (119 to 130 d of gestation) served as sham-operated controls. The same operative procedures were carried out, except for the SAD procedure. On the day of surgery and each day thereafter, the ewe received 2×10^6 IU of penicillin G and 800 mg of kanamycin sulfate, half i.v. and half into the amniotic cavity.

Experimental protocol. Studies were performed on the 3rd to 4th postoperative days while the ewe stood in a study cage. Fetal phasic and mean arterial pressures were measured with Statham P23Db strain gauge transducers (Statham Instruments, Oxnard, CA) and were recorded on a Beckman direct-writing polygraph throughout the experiment. Amniotic fluid pressure was used as a zero reference for fetal vascular pressures. Blood samples from the descending aorta of the fetus were analyzed on a Radiometer blood gases analyzer (HM73; London Co., Oakland, CA) for the determination of blood gases and pH.

By the radionuclide-labeled microsphere technique, fetal cardiac output and blood flow distribution were determined by simultaneous injection of two differently labeled microspheres into the inferior and superior vena cavae of the fetus while reference samples were withdrawn at a rate of 3.5 to 4.0 mL/min from the descending aorta and carotid artery. The volume of blood removed was replaced with an equal volume of fetal or maternal blood at the time of sampling. The 15-μm microspheres were labeled with ^{153}Gd, ^{57}Co, ^{51}Cr, ^{113}Sn, ^{85}Sr, ^{125}I, ^{46}Sc, ^{95}Nb, ^{65}Zn, or ^{54}Mn. Fetuses were then made hypoxemic by allowing the ewe to breathe 10% O_2 and 3% CO_2 for a period of 20 min, after which the sampling of blood and injection of microspheres were repeated.

Measurements and analysis of data. At the end of the studies, the ewe was anesthetized with an i.v. injection of pentobarbital sodium and killed with an injection of saturated KCl solution. The fetuses were removed and dissected. Fetal tissues were incinerated in an oven and counted for radioactivity in a 1000-channel computerized pulse height analyzer (Ino-Tech Inc., Fort Atkinson, WI). Blood flow was calculated from the tissue counts and reference sample data (24, 25).

Organ vascular resistance was calculated as the ratio of mean arterial pressure (at the time of microsphere injection) and organ blood flow. Rate-pressure product, an index of myocardial oxygen consumption, was calculated as the fetal heart rate times systolic arterial pressure (26, 27).

Fetal heart rate and blood pressure responses were determined by recording the values of heart rate and blood pressure at 1-min intervals before and during the period of hypoxemia; data were analyzed by one-way analysis of variance for repeated measures. Mean values for blood flows, blood gases, and pH, as well as organ vascular resistances during both control and hypoxemia, were compared by paired or unpaired t test for or between group differences, respectively.

RESULTS

Control values for fetal blood gases, pH, heart rate, and arterial pressure were within the normal range and were similar in intact and SAD fetuses. Maternal hypoxemia significantly decreased P_{O_2} in fetal blood, but no significant changes in P_{CO_2} or blood pH were observed (Table 1). Mean fetal heart rate and arterial pressure before hypoxemia and during hypoxemia, at the time of microsphere injection, are shown in Table 1. Fetal heart rate decreased in the intact fetuses but increased in the SAD fetuses. Arterial blood pressure increased significantly in both groups. The fetal heart rate and blood pressure responses to hypoxemia (Fig. 1) were also analyzed at 1-min intervals. In the intact fetuses, heart rate decreased ($p < 0.001$) to a trough value 3 min after the onset of hypoxemia and gradually recovered thereafter, whereas it increased after 9 min of hypoxemia in the SAD fetuses ($p < 0.05$). Hypoxemia produced a rise in arterial pressure in both groups of animals; the increase in mean arterial pressure was statistically significant ($p < 0.01$) only in the SAD fetuses. The time course of blood pressure response differed; an early hypertensive response was noted in the intact fetuses, but blood pressure transiently decreased with the onset of hypoxemia in the SAD fetuses and then progressively increased during the period of hypoxemia (Fig. 1).

During hypoxemia, there was no significant change in the rate-pressure product in the intact fetuses. However, it increased 38% in the SAD fetuses (Table 1), suggesting an increased cardiac work load in these fetuses.

There were no significant differences between control and SAD fetuses in combined ventricular output and umbilical blood flow during normoxia. Acute hypoxemia had no significant effect on these values (Table 2). During hypoxemia in the intact fetuses, blood flow increased to the brain, heart, and adrenals but decreased 39% to the periphery (skin, muscle, and bone). Pulmonary blood flow decreased 33%, but the change was not significant because of large variance. Similar changes in organ blood flows were observed in the SAD fetuses, except that blood flow to the periphery was maintained during hypoxemia (Table 2). The change in peripheral blood flow during hypoxemia was significantly different between the control and denervated fetuses ($p < 0.05$). Also, the change in the proportion of cardiac output distributed to the periphery was significantly different between the two groups ($p < 0.01$). The calculated resistances in the

Table 1. *Fetal arterial blood gases, pH, heart rate, blood pressure, and rate-pressure product during control and hypoxemia**

	Intact fetuses ($n = 9$)		SAD fetuses ($n = 8$)	
	Control	Hypoxemia	Control	Hypoxemia
P_{O_2}				
(torr)	22 ± 3	12 ± 2†	21 ± 2	12 ± 2†
(kPa)	2.9 ± 0.4	1.6 ± 0.3†	2.8 ± 0.3	1.6 ± 0.3†
P_{CO_2}				
(torr)	41 ± 1	40 ± 3	41 ± 3	43 ± 4
(kPa)	5.5 ± 0.1	5.3 ± 0.4	5.5 ± 0.4	5.7 ± 0.5
pH	7.40 ± 0.01	7.38 ± 0.01	7.38 ± 0.03	7.36 ± 0.05
Heart rate (beats/min)	184 ± 12	165 ± 23†	184 ± 22	200 ± 16†
MAP				
(torr)	45 ± 6	54 ± 6†	41 ± 9	49 ± 12†
(kPa)	6.0 ± 0.8	7.2 ± 0.8†	5.5 ± 1.2	6.5 ± 1.6†
RPP (torr·beats·min^{-1})	10 363 ± 1557	11 608 ± 2163	10 204 ± 1502	14 051 ± 3272†‡
RPP (kPa·beats·min^{-1})	1381 ± 208	1547 ± 288	1360 ± 200	1873 ± 436†‡

* Values are means ± SD. MAP, mean aortic pressure; RPP, rate-pressure product.

† $p < 0.05$ (within-group differences) (paired t test).

‡ $p < 0.05$ (between-group differences) (unpaired t test).

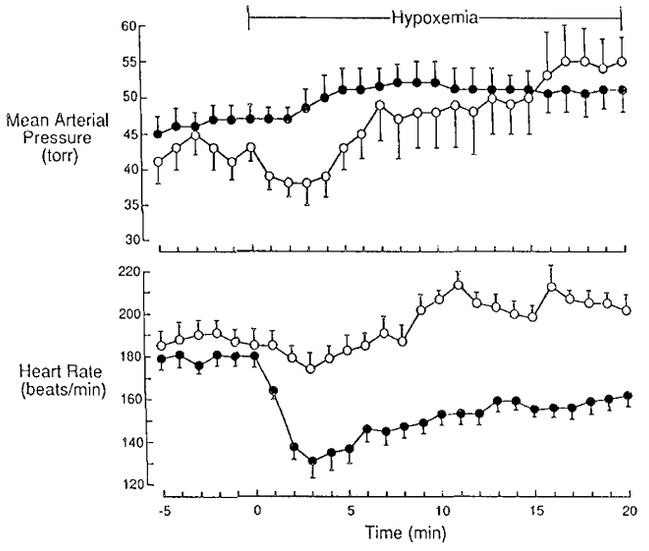

Fig. 1. Fetal heart rate and mean arterial pressure (conversion factor to kPa = 0.1333) responses to hypoxemia in intact (●) and SAD (○) fetuses. Data are represented as means ± SEM. Fetal heart rate fell ($p < 0.001$) 2 min after the onset of hypoxemia in the intact fetuses but increased ($p < 0.05$) after 10 min of hypoxemia in the denervated fetuses. Mean arterial pressure increased ($p < 0.01$) after 15 min in the denervated fetuses; the increase in mean arterial pressure in the intact fetuses was not statistically significant.

Table 2. *Fetal combined ventricular output and organ blood flow before and during hypoxemia**

	Intact fetuses ($n = 9$)		SAD fetuses ($n = 8$)	
	Control	Hypoxemia	Control	Hypoxemia
CVO (mL·min^{-1}·kg^{-1})	516 ± 84	524 ± 130	570 ± 72	614 ± 61‡
Umbilical blood flow (mL·min^{-1}·kg^{-1})	251 ± 59	283 ± 85	239 ± 40	264 ± 39
Fetal body flow (mL·min^{-1}·kg^{-1})	265 ± 52	241 ± 95	327 ± 51‡	350 ± 60‡
Distribution of cardiac output (%)				
Brain	4.7 ± 1.9	8.8 ± 3.1†	4.4 ± 0.9	7.3 ± 3.0†
Heart	3.2 ± 1.5	8.0 ± 3.5†	3.0 ± 0.9	8.0 ± 2.7†
Periphery	30.4 ± 5.8	16.9 ± 7.2†	30.7 ± 4.8	28.0 ± 7.1‡
Placenta	48.4 ± 7.2	54.6 ± 13.6	42.0 ± 5.4	43.1 ± 6.2‡
Kidneys	2.1 ± 0.7	1.9 ± 1.0	2.7 ± 1.1	2.6 ± 0.8
Gut	3.9 ± 1.5	2.9 ± 1.9	5.8 ± 2.1‡	5.1 ± 1.3‡
Spleen	1.2 ± 1.4	0.7 ± 0.7	1.3 ± 0.7	0.7 ± 0.5†
Liver	0.4 ± 0.6	0.4 ± 0.6	0.7 ± 0.6	1.1 ± 1.2
Lungs	6.0 ± 2.8	4.1 ± 3.2	7.6 ± 1.6	3.6 ± 1.2†
Organ blood flow (mL·min^{-1}·100 g^{-1})				
Brain	122 ± 43	214 ± 71†	120 ± 33	202 ± 61†
Heart	255 ± 132	666 ± 360†	228 ± 57	670 ± 202†
Periphery	23 ± 4	14 ± 7†	25 ± 4	25 ± 7‡
Adrenals	357 ± 270	953 ± 470†	302 ± 150	851 ± 29†
Kidneys	145 ± 51	140 ± 79	181 ± 53	191 ± 57
Gut	78 ± 29	61 ± 39	116 ± 42‡	110 ± 30‡
Spleen	433 ± 487	280 ± 253	534 ± 286	291 ± 222†
Liver	22 ± 30	6 ± 7	12 ± 10	18 ± 16
Lungs	112 ± 59	75 ± 58	178 ± 56	87 ± 40†

* Values are means ± SD. CVO, combined ventricular output.
† $p < 0.05$ (within-group differences) (paired t test).
‡ $p < 0.05$ (between-group differences) (unpaired t test).

peripheral circulation increased during hypoxemia in the intact fetuses but did not change significantly in the SAD fetuses. The changes in vascular resistances in other organs are shown in Table 3 and, in general, were similar in the two groups.

DISCUSSION

These studies indicate that the arterial chemoreflex is important in directly mediating some of the fetal cardiovascular responses to acute hypoxemia. In agreement with previous studies, we have shown that the normal integrated response of the fetal circulation to acute hypoxemia includes bradycardia, peripheral vasoconstriction, and redistribution of cardiac output to favor the heart, brain, and adrenals and to maintain umbilical blood flow (1).

Denervation of the aortic and carotid bodies abolished bradycardia and peripheral vasoconstriction during hypoxemia, indicating that the fetal arterial chemoreflex directly mediates the normal increase in vagal tone, with slowing of the heart rate, and increase in sympathetic nervous system activity with resultant peripheral vasoconstriction. That the elimination of bradycardia in SAD fetuses is due to removal of the well-characterized chemoreflex-mediated increased vagal tone (6, 8, 19, 20, 22) and not to removal of sympathetic tone, is supported by the observation in sympathectomized fetal sheep of acute hypoxemia-induced slowing of fetal heart rate (2).

Although baroreceptors are also denervated in the SAD procedure, it is unlikely that the bradycardia was abolished because these baroceptors were removed. We have shown previously that bradycardia results during fetal hypoxemia before any increase in arterial pressure (6). Possibly, hypertension contributes to the bradycardia in the later phase of hypoxemia and the tachycardia occurring in the later period in the SAD fetuses could be partly related to abolition of the baroreflexes. The tachycardia that began to appear 8 to 10 min after the onset of hypoxemia in the denervated fetuses can probably be accounted for by a response to increased catecholamine concentrations. Although SAD may abolish neural stimulation of adrenal catecholamine release, hypoxemia has a direct effect on the adrenal glands in invoking catecholamine secretion (10). Also, in fetal lambs in which sympathetic nerve endings were destroyed by 6-hydroxydopamine administration, plasma catecholamine concentrations increased similarly to those in normal fetuses (2).

Peripheral vasoconstriction during hypoxemia was virtually eliminated in the SAD fetuses; nevertheless, a significant increase in blood pressure was observed. However, this hypertensive response not only was delayed compared with the normal early increase in blood pressure observed in the intact fetuses, but was also preceded by a transient decrease in blood pressure (Fig. 1). The mechanism underlying this progressive, delayed hypertensive response in the SAD fetuses is not clear. In fetal sheep, acute hypoxemia stimulates the secretion of vasopressin and catecholamines (10–12); possibly, the increase in blood pressure is related to these humoral factors. It is not known whether SAD modified basal or hypoxic-stimulated release of these hormones in the fetus. In adult dogs, the augmented increase of angiotensin II during hypoxemia is independent of carotid chemoreceptor activity (28) whereas the increase in vasopressin during hypoxia is mediated by the peripheral chemoreceptors (29).

CNS or spinal mechanisms could also be involved in the hypertensive response to hypoxemia. In adult animals, hypoxia activates both antagonistic excitatory and inhibitory processes acting on sympathetic neurons independent of peripheral chemoreceptors (30, 31). If such mechanisms do exist in the fetus, their effect probably is small because only a small and not significant increase in peripheral vascular resistance occurred in the SAD fetuses. It is possible, however, that these central and spinal mechanisms are activated during hypoxia more severe than that achieved in this study.

Vascular responses to hypoxemia in the brain, heart, adrenals,

Table 3. *Fetal vascular resistances before and during hypoxemia (kPa·mL^{-1}·min·100 g of tissue)**

	Intact fetuses (n = 9)		SAD fetuses (n = 8)	
	Control	Hypoxemia	Control	Hypoxemia
Brain	0.053 ± 0.017	0.036 ± 0.015†	0.052 ± 0.015	0.043 ± 0.029
Heart	0.028 ± 0.011	0.013 ± 0.008†	0.024 ± 0.005	0.009 ± 0.003†
Periphery	0.273 ± 0.061	0.521 ± 0.299†	0.223 ± 0.041	0.299 ± 0.193
Adrenals	0.032 ± 0.025	0.009 ± 0.005†	0.021 ± 0.009	0.008 ± 0.003†
Kidneys	0.044 ± 0.012	0.051 ± 0.023	0.035 ± 0.017	0.037 ± 0.019
Gut	0.089 ± 0.044	0.185 ± 0.248	0.059 ± 0.027	0.064 ± 0.037
Total fetal body (kPa·mL^{-1}·min·kg)	0.024 ± 0.005	0.035 ± 0.019†	0.017 ± 0.004‡	0.019 ± 0.008‡

* Values are means ± SD.

† $p < 0.05$ (within-group differences) (paired t test).

‡ $p < 0.05$ (between-group differences) (unpaired t test).

and lungs seem to be mediated not by hypoxic stimulation of the arterial chemoreceptors, but rather by local mechanisms, because similar responses in these vascular beds were observed in the intact and the SAD fetuses (Table 2). There is considerable controversy surrounding the control of myocardial and cerebral flow and vascular resistance by the arterial chemoreflex of the adult, although the results from several studies suggest that the vascular responses to hypoxemia in these organs are largely mediated by local mechanisms (reviewed in Ref. 13). In the fetus, myocardial and cerebral blood flow are related to the reciprocal of arterial oxygen concentration, permitting the fetus to maintain a constant oxygen delivery and consumption in these organs (32–34). Fetal pulmonary vasculature is exceedingly sensitive to changes in Po_2 and pulmonary blood flow is related to the level of pulmonary arterial Po_2 (35).

In the study presented here, only a small, insignificant decrease in blood flow to the gastrointestinal tract was observed in the intact fetuses. More severe hypoxemia has been shown to decrease blood flow to the vascular bed significantly (1). Studies in adult dogs suggest that the carotid chemoreceptors control mesenteric vasoactivity during hypoxemia (13, 36). It is difficult to conclude from this study whether the arterial chemoreflex mediates the mesenteric vasoconstrictive response to hypoxemia in the fetus through activation of the peripheral nerve terminals of the sympathetic nervous system. The response during severe hypoxia could be related to hormonal influence.

Similarly, on the basis of our study, it is difficult to conclude whether the arterial chemoreflex plays a role in regulating fetal renal blood flow during hypoxemia. The fetal and adult renal vascular bed is less sensitive to hypoxic stimulation as shown in this and previous studies (33, 36, 37). The relative sparing of the renal vasculature appears to be related to mechanisms involving prostaglandins counteracting the sympathetic vasoconstriction (3, 38). This neural vasoconstriction has been shown to be mediated by hypoxic stimulation of the carotid chemoreceptors of the adult dog (36).

Although the arterial chemoreceptors are involved in some of the fetal cardiovascular responses to acute hypoxemia, one may wonder whether the arterial chemoreflex is crucial for fetal survival during acute hypoxemia. Umbilical blood flow and oxygen delivery to vital fetal organs were maintained in the SAD fetuses. Because arterial blood pH level was maintained, it is unlikely that significant tissue hypoxia occurred, resulting in increased lactic acid production. In conclusion, the arterial chemoreceptors do not appear to be crucial for the immediate survival of the fetus during acute hypoxemia, at least of the severity and duration employed in this study. However, they do result in peripheral vasoconstriction and thus contribute to maintenance of umbilical-placental blood flow during hypoxemia. Also, by inducing bradycardia, they reduce the rate-pressure product and, thus, myocardial oxygen consumption during fetal hypoxic stress.

REFERENCES

1. Cohn HE, Sacks EJ, Heymann MA, Rudolph AM 1974 Cardiovascular responses to hypoxemia and acidemia in fetal lambs. Am J Obstet Gynecol 120:817–824
2. Iwamoto HS, Rudolph AM, Mirkin BL, Keil LC 1983 Circulatory and humoral responses of sympathectomized fetal sheep to hypoxemia. Am J Physiol 245:H767–H772
3. Robillard JE, Nakamura KT, Dibona GF 1986 Effects of renal denervation on renal responses to hypoxemia in fetal lambs. Am J Physiol 250:F294–F301
4. Tabsh K, Nuwayhid B, Murad S, Ushioda E, Erkkola R, Brinkman III CR, Assali NS 1982 Circulatory effects of chemical sympathectomy in fetal, neonatal, and adult sheep. Am J Physiol 243:H113–H122
5. Cohn HE, Piasecki GJ, Jackson BT 1980 The effect of fetal heart rate on cardiovascular function during hypoxemia. Am J Obstet Gynecol 138:1190–1199
6. Itskovitz J, Goetzman BW, Rudolph AM 1982 The mechanism of late deceleration of the heart rate and its relationship to oxygenation in normoxemic and chronically hypoxemic fetal lambs. Am J Obstet Gynecol 142:66–73
7. Parer JT, Krueger TR, Harris JL 1980 Fetal oxygen consumption and mechanisms of heart rate response during artificially produced late deceleration of fetal heart rate in sheep. Am J Obstet Gynecol 135:637–646
8. Walker AM, Cannata JP, Dowling MH, Ritchie BC, Malone JE 1979 Age-dependent pattern of autonomic heart rate control during hypoxia in fetal and newborn lambs. Biol Neonate 35:198–208
9. Cohen WR, Piasecki GJ, Jackson BT 1982 Plasma catecholamines during hypoxemia in fetal lamb. Am J Physiol 243:R520–R525
10. Comline RS, Silver M 1961 The release of adrenaline and noradrenaline from the adrenal glands of the foetal sheep. J Physiol (Lond) 156:424–444
11. Rurak DW 1978 Plasma vasopressin levels during hypoxemia and the cardiovascular effects of exogenous vasopressin in fetal and adult sheep. J Physiol (Lond) 277:341–357
12. Robillard JE, Weitzman RE, Burmeister L, Smith Jr FG 1981 Developmental aspects of the renal response to hypoxemia in the lamb fetus. Circ Res 48:128–138
13. Daly MdB 1983 Peripheral arterial chemoreceptors and the cardiovascular system. In: Acker H, O'Regan RG (eds) Physiology of the Peripheral Arterial Chemoreceptors. Elsevier Science Publishers, New York, pp 325–393
14. Biscoe TJ, Purves MJ, Sampson SR 1969 Types of nervous activity which may be recorded from the carotid sinus nerve of the sheep foetus. J Physiol (Lond) 202:1–24
15. Blanco CE, Dawes GS, Hanson MA, McCooke HB 1984 The response to hypoxia of arterial chemoreceptors in fetal sheep and new-born lambs. J Physiol (Lond) 351:25–37
16. Dawes GS, Lewis BV, Milligan JE, Roach MR, Talner NS 1968 Vasomotor responses in the hind limb of foetal and newborn lambs to asphyxia and aortic chemoreceptor stimulation. J Physiol (Lond) 195:55–81
17. Dawes GS, Duncan SB, Lewis BV, Merlet CL, Owen-Thomas JB, Reeves JT 1969 Cyanide stimulation of the systemic arterial chemoreceptors in foetal lambs. J Physiol (Lond) 201:117–128
18. Dawes GS, Duncan SLB, Lewis GV, Merlet CL, Owen-Thomas JB, Reeves JT 1969 Hypoxemia and aortic chemoreceptor function in foetal lambs. J Physiol (Lond) 201:105–116
19. Itskovitz J, Rudolph AM 1982 Denervation of arterial chemoreceptors and baroreceptors in fetal lambs *in utero*. Am J Physiol 242:H916–H920
20. Itskovitz J, Rudolph AM 1987 Cardiorespiratory response to cyanide of arterial chemoreceptors in fetal lambs. Am J Physiol 252:H916–H922
21. Ponte J, Purves MJ 1973 Types of afferent nervous activity which may be measured in the vagus nerve of the sheep foetus. J Physiol (Lond) 229:51–56
22. Koos BJ, Sameshima H 1988 Effects of hypoxaemia and hypercapnia on breathing movements and sleep state in sinoaortic-denervated fetal sheep. J Dev Physiol 10:131–144
23. Itskovitz J, LaGamma EF, Rudolph AM 1983 Baroreflex control of the circulation in chronically instrumented fetal lambs. Circ Res 52:589–596
24. Heymann MA, Payne BD, Hoffman JIE, Rudolph AM 1977 Blood flow

measurements with radionuclide-labeled particles. Prog Cardiovasc Dis 20:55–79
25. Rudolph AM, Heymann MA 1967 The circulation of the fetus *in utero*. Methods for studying distribution of blood flow, cardiac output and organ blood flow. Circ Res 21:163–184
26. Fisher DJ, Heymann MA, Rudolph AM 1982 Fetal myocardial oxygen and carbohydrate consumption during acutely induced hypoxemia. Am J Physiol 242:H657–H661
27. Kitamura KCR, Jorgensen CR, Gobel FL, Taylor HL, Wang Y 1972 Hemodynamic correlates of myocardial oxygen consumption during upright exercise. J Appl Physiol 32:516–522
28. Raff H, Shinsako J, Dallman MF 1987 Renin and ACTH responses to hypercapnia and hypoxia after chronic chemodenervation. Am J Physiol 247:R412–R417
29. Handley DF, Wilson DA, Feldman MA, Traystman RJ 1988 Peripheral chemoreceptor control of neurohypophysial blood flow. Am J Physiol 254:H742–H750
30. Bernthal T, Woodcock CC 1951 Responses of the vasomotor center to hypoxia after denervation of the carotid and aortic bodies. Am J Physiol 166:45–54
31. Rohlicek CV, Polosa C 1983 Hypoxic responses of sympathetic preganglionic neurons in sinoaortic-denervated cats. Am J Physiol 244:H681–H686
32. Jones Jr MD, Sheldon RE, Peeters LL, Makowski EL, Meschia G 1978 Regulation of cerebral blood flow in the ovine fetus. Am J Physiol 235:H162–H166
33. Peeters LLH, Sheldon RE, Jones MD, Makowski EL, Meschia G 1979 Blood flow to fetal organs as a function of arterial oxygen content. Am J Obstet Gynecol 135:637–646
34. Sheldon RE, Peeters LLH, Jones Jr MD, Makowski EL, Meschia G 1979 Redistribution of cardiac output and oxygen delivery in the hypoxemic fetal lamb. Am J Obstet Gynecol 135:1071–1078
35. Lewis AB, Heymann MA, Rudolph AM 1976 Gestational changes in pulmonary vascular responses in fetal lambs *in utero*. Circ Res 39:536–541
36. Rutherford JD, Vatner SF 1978 Integrated carotid chemoreceptor and pulmonary inflation reflex control of peripheral vasoactivity in conscious dogs. Circ Res 43:200–208
37. Reuss ML, Parer JT, Harris JL, Krueger TR 1982 Hemodynamic effects of alpha-adrenergic blockade during hypoxia in fetal sheep. Am J Obstet Gynecol 142:410–415
38. Millard RW, Baig H, Vatner SF 1979 Prostaglandin control of the renal circulation in response to hypoxemia in the fetal lamb *in utero*. Circ Res 45:172–179