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Distribution of Cardiac Output in Fetal and Neonatal Lambs with Acute Respiratory Acidosis

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Summary

The effects of changes in $Paco_2$ on the circulation are complex, involving local vasodilation, vasodilation mediated by the pulmonary inflation reflex, and vasoconstriction due to effects on central vasomotor centers and peripheral chemoreceptors. One might anticipate that some or all of these might differ between the fetus *in utero* and the newborn. Distribution of cardiac output was measured in unanesthetized fetal ($n = 6$) and newborn ($n = 7$) sheep, using the radioactive microsphere technique. $Paco_2$ rose from 44 to 70 (fetus) and 38 to 60 torr (newborn) with the addition of CO_2 to room air. In the fetus, there were significant increases in central nervous system (CNS), diaphragm, and lung blood flows. No organ showed a significant decrease in flow. Local vasodilation by CO_2 was the likely cause of the increased flow to CNS. The large increase in pulmonary blood flow was most likely due to the associated rise in fetal Pao_2 (23 to 28 torr) that accompanied respiratory acidosis and the presence of fetal breathing movements. The rise in diaphragmatic blood flow was likely the result of fetal breathing. In the newborn, CNS and diaphragm flows rose, but unlike the fetus, spleen and stomach flows decreased. These decreased flows in the hypercapnic newborn may have been due to stimulation of either central vasomotor centers or peripheral chemoreceptors.

Abbreviations

CNS, central nervous system
DAo, descending aorta
DA, ductus arteriosus
I, aortic isthmus
PA, pulmonary artery
$\dot{Q}$, blood flow
***C*, radioactive counts**

Studies of the redistribution of cardiac output induced by hypoxia in fetal and adult animals (1, 4, 10) have shown that cardiac, cerebral, and adrenal oxygen delivery is preserved at the expense of other organs. Redistribution is accomplished by a local effect of hypoxia which dilates cerebral and coronary vessels, while the chemoreceptor reflex produces vasoconstriction in skeletal muscle and splanchnic beds (16).

The circulatory effects of changes in $Paco_2$, on the other hand, have not been as carefully studied. In particular, there are no data comparing effects before and after birth. The response of cardiac output and its regional distribution to changes in $Paco_2$ has been looked at in an acute fetal preparation but blood flow was measured only in major arteries (3). Only recently has the regional blood flow response been described in quantitative detail in a conscious adult animal (21). These studies done on adult sheep have shown that the effect of CO_2 on the circulation is nonlinear. Cardiac output is unchanged as $Paco_2$ increases from 36 to 58 mm Hg; however, a 35% increase occurs as $Paco_2$ is further increased to 75 mm Hg. Nonlinearity characterized some of the responses of regional blood flows as well. These variable responses are not surprising when one considers that regional blood flow in hypercapnia depends upon complex interactions of a number of factors including local vasodilation by CO_2 (7, 9, 13, 20, 29), vasodilation mediated by the pulmonary inflation reflex (12, 32), vasoconstriction induced by a central effect of CO_2 on vasomotor centers (15), and vasoconstriction induced by effects on peripheral chemoreceptors (27). Given the complicated nature of these interactions, one might anticipate considerable differences in the response to respiratory acidosis before and after birth. Therefore, in conjunction with studies on developmental differences in the response of the cerebral circulation to CO_2 (30), we have studied the distribution of cardiac output in the fetal and neonatal lamb after the induction of acute respiratory acidosis.

MATERIALS AND METHODS

Preparation. Six fetal lambs (128–132 days of gestation with term at 145 days) and seven newborn lambs (age 3–10 days) were studied. All animals were of mixed breed. Time-dated ewes with singleton pregnancies were operated upon under halothane anesthesia. The uterus was exposed by a midline abdominal incision. The extremities of the fetus were exposed through uterine incisions. Polyvinyl chloride catheters (0.034-inch ID × 0.054-in OD; Martech Medical Products, Lansdale, PA) were placed into the fetal inferior vena cava (via a pedal vein), the abdominal aorta (via pedal artery), and the brachiocephalic artery (via an axillary artery). The position of the catheter in the brachiocephalic artery was standardized as previously described (30). Tygon tubing (1/16-in ID × 1/8-in OD; Norton Plastics, Akron, OH) was placed into the amniotic cavity. Uterine and abdominal incisions were then closed, and the catheters were exteriorized through the ewe's flank. All ewes were allowed 72 h to recover prior to study.

The lambs were operated upon under pentobarbital anesthesia. Polyvinyl chloride catheters (as above) were placed into the abdominal aorta (via femoral artery), and into the brachiocephalic artery and left ventricle (via an axillary artery). When the lambs awoke from anesthesia, they were returned to their mothers. They were studied 24 h later. At that time, all lambs were standing and feeding normally.

Measurements. Total cardiac output and individual organ flows were measured using the radioactive microsphere technique (18, 28). In each animal, flows were measured while the animal breathed room air, and again while breathing an increased inspired CO_2 concentration. Radioactive microspheres (approximately $1.0–1.5 \times 10^6$ (15 μm in diameter) labeled with ^{85}Sr,

^{95}Nb, ^{46}Sc, or ^{141}Ce (3M, St. Paul, MN) were injected over 1.5 min from a continuously stirred mixture of approximately 300,000 microspheres/ml into the inferior vena cava of the fetus and left ventricle of the newborn lamb. Meanwhile, reference blood samples were withdrawn from the brachiocephalic artery and abdominal aorta at a rate of 1.30 ml·min^{-1} with a pump (Harvard Apparatus, Dover, MA). Withdrawal began 2 min before microsphere injection and continued for 1 min after it was completed. Microsphere injections were not associated with changes in blood pressure and heart rate. Individual organ flows were calculated according to the following equation $\dot{Q}_0 = cpm_0/cpm_r \times \dot{Q}_r$ where $\dot{Q}_0$ is organ blood flow (ml·100 g^{-1} min^{-1}), cpm_0 is cpm·100 g^{-1} in the organ tissue sample, cpm_r is counts/min in the reference blood sample, and $\dot{Q}_r$ is the withdrawal rate of the reference sample (ml·min^{-1}). The brachiocephalic artery reference sample was used to calculate flows to the heart, brain, and upper body carcass and skin. The abdominal aorta reference sample was used to calculate flows to the lungs (bronchial arterial flow in the lamb), diaphragm, liver, spleen, adrenals, kidneys, gastrointestinal tract, lower body carcass, skin, and placenta (in the fetus). Lung flow calculated from the reference artery microsphere technique can be falsely elevated if there is shunting of microspheres through the systemic circulation. During injections, blood was withdrawn from a sagittal sinus catheter which had been placed in each animal for measurement of cerebral venous oxygen content for a coincident study (30). Significant microsphere numbers were not detected in either the control or hypercarbic states.

The abdominal aorta catheter is not the ideal reference catheter to calculate pulmonary blood flow in the fetus. A right ventricular or, even better, a pulmonary artery catheter is more appropriate (17). However, the abdominal aorta catheter has a reproducible relationship to a pulmonary artery reference sample, and should be adequate to assess large changes in lung blood flow.

The descending aorta (DAo) is a mixture of blood from the pulmonary artery via the ductus arteriosus (DA) [82% of DAo flow (2)] and from the aortic isthmus (I) [18% of DAo flow (2)].

$$\dot{Q}\mathrm{DAo} = \dot{Q}\mathrm{DA} + \dot{Q}\mathrm{I} \quad (1)$$

where $\dot{Q}$ = flow (ml·min^{-1}). Then

$$\dot{Q}\mathrm{DAo}(C\mathrm{DAo}) = \dot{Q}\mathrm{DA}(C\mathrm{PA}) + \dot{Q}\mathrm{I}(C\mathrm{I}) \quad (2)$$

where C represents radioactive counts·ml^{-1} in the same arterial streams and PA represents pulmonary artery.

In our study, the ratio between the brachiocephalic artery (representative of CI) and the descending aorta microsphere concentrations were 1.2 and 1.03 in control and hypercapnia respectively. Therefore

$$\dot{Q}\mathrm{DAo}(C\mathrm{DAo}) = \dot{Q}\mathrm{DA}(C\mathrm{PA}) + \dot{Q}\mathrm{I}(1.2C\mathrm{DAo}) \quad (3)$$

$$\dot{Q}\mathrm{DAo}(C\mathrm{DAo}) = \dot{Q}\mathrm{DA}(C\mathrm{PA}) + \dot{Q}\mathrm{I}(1.03C\mathrm{DAo}) \quad (4)$$

Rearranging to solve for the ratio of CPA/CDAo:

$$C\mathrm{PA}/C\mathrm{DAo} = (\dot{Q}\mathrm{DAo} - 1.2\dot{Q}\mathrm{I})/\dot{Q}\mathrm{DA} \quad (3a)$$

$$C\mathrm{PA}/C\mathrm{DAo} = (\dot{Q}\mathrm{DAo} - 1.03\dot{Q}\mathrm{I})/\dot{Q}\mathrm{DA} \quad (4a)$$

One can then substitute known values (2) for the relative flows in the various vessels as percentages of fetal cardiac output: $\dot{Q}$DAo = 66%, $\dot{Q}$DA = 54%, $\dot{Q}$I = 12%. Solving for CPA/CDAo yields a ratio of 0.96 and 0.99 for control and hypercapnia, respectively. Thus, under these circumstances, CDAo $\simeq$ CPA for calculation of lung blood flow. This will always be true when the ratio of microsphere concentrations above and below the ductus is near 1 as it was in our experiment. At higher ratios, the error will depend on the proportion of DAo blood from the isthmus. At a CI/CDAo of 1.2, the CPA/CDAo would still be 0.89, even in the unlikely event that the relative isthmus contribution doubled.

Cardiac output was determined by summing the total flows to the individual organs, carcass, and skin. The radioactivity in each sample was determined using a two-channel γ-counter (Tracor Analytic, Des Plaines, IL). The tissues were prepared as described by Peeters *et al.* (28) with the exception that we used a 2-cm sample height in the counting vials. Adequate mixing of microspheres was confirmed at the organ level by comparison of right and left cerebral hemispheres, right and left kidneys, and upper and lower body skin. At the reference sample level, mixing was confirmed by validation studies comparing multiple brachiocephalic artery and abdominal aorta catheters. We also were unable to demonstrate a difference between left atrial and left ventricular injections in the lamb. All reference blood samples and tissues contained greater than 400 microspheres (8).

Blood samples for pH, arterial CO_2 tension ($Paco_2$), arterial O_2 tension (Pao_2), and hematocrit were withdrawn anaerobically into heparinized Natelson glass pipettes from the brachiocephalic artery (lamb and fetuses) and abdominal aorta (fetuses). Oxygen contents were measured using the Lex-O_2-Con-TL (Lexington Instruments, Walthan, MA). Pao_2, $Paco_2$, and pH were measured at 39.5°C using the Radiometer BMS3 MK2 (Radiometer, Copenhagen). Blood pressure and heart rate were continuously monitored in the abdominal aorta (Gould Instruments, Oxnard, CA). In the lamb, the blood pressure was referenced to the right atrium and in the fetus to the amniotic fluid pressure.

Experimental Protocol. On the day of the experiment, the ewes (fetal studies) and lambs had opaque plastic bags placed over their heads to control the inspired gas composition. The bag was filled with a constant flow of room air to which CO_2 was added in varying percentage (0–10%) to obtain the desired $Paco_2$ for 10 min. Blood gases and oxygen contents were drawn before and after each microsphere injection. In both the fetuses and lambs, individual organ flows and total cardiac output were ascertained in the control and hypercarbic states. Comparisons between control and hypercarbic conditions in the fetus and the lamb for blood gases, oxygen contents, blood pressure, and heart rate were made using paired t tests with a Bonferroni correction (33). The critical Bonferroni value (t^*) at $P < 0.05$ was 2.99 in fetuses and 2.93 in the lambs. Comparisons of individual organ flows and cardiac output between control and hypercarbia were also calculated with paired t tests with a Bonferroni correction (t^* at $P < 0.05$–3.20 for fetuses, 3.19 for lambs.

RESULTS

Physiologic Measurements. Baseline and hypercarbic physiologic measurements are presented in Table 1 (fetuses) and Table 2 (lambs). In the fetus, increases in $Paco_2$ resulted in significant increases in Pao_2 in both the brachiocephalic artery (α_1) and abdominal aorta (α_2) due to the rightward shift in both the maternal fetal oxyhemoglobin dissociation curves (23, 24). There were no changes in Cao_2, blood pressure, or heart rate. In the lamb, increases in $Paco_2$ also resulted in a significant increase in systemic Pao_2, probably caused by hyperventilation and expansion of atelectatic areas with improvement in ventilation perfusion relationship. Cao_2, blood pressure, and heart rate were unchanged.

Total Cardiac Output. Total cardiac output was not significantly different (426 ± 33 and 410 ± 33 ml·kg^{-1} min^{-1}; mean ± SEM) during control and hypercarbic states in the lambs (Fig. 1). In the fetus, it rose in five of six animals, but this was not significantly different (433 ± 20 and 494 ± 29 ml·kg^{-1} min^{-1}; mean ± SEM).

Individual Organ Blood Flows. In the fetus, flows (ml·100 g^{-1} min^{-1}) to cerebral cortex, cerebellum, and brainstem were significantly increased as previously reported (30). In addition, diaphragm and lung blood flows rose significantly (Table 3).

In the lamb, flows (ml·100 g^{-1} min^{-1}) to cerebral cortex, cerebellum, and brainstem were significantly increased once again as previously reported (30). As in the fetus, diaphragm flow increased significantly. Flows to spleen and stomach were sig-

Table 1. *Physiologic measurements: fetuses**

	Pa_{O_2}-α_1 (mm Hg)	Pa_{O_2}-α_2 (mm Hg)	Pa_{CO_2} (mm Hg)	pH	Ca_{O_2}-α_1 (vol%)	Blood pressure (mm Hg)	Heart rate (min^{-1})
Control	26.3 ± 1.5	23.0 ± 0.7	44.3 ± 1.2	7.38 ± .02	9.85 ± 0.32	49 ± 2.3	155 ± 10
Hypercarbia	31.2 ± 1.3†	28.0 ± 0.8†	70.0 ± 2.3†	7.24 ± .01†	9.83 ± 0.38	48 ± 2.7	143 ± 8

* Mean ± SE for $n = 6$ determinations; α_1, brachiocephalic artery; α_2, abdominal aorta.
† $P < 0.05$ using critical Bonferroni value of $t^* = 2.99$.

Table 2. *Physiologic measurements: lambs**

	Pa_{O_2} (mm Hg)	Pa_{CO_2} (mm Hg)	pH	Ca_{O_2} (vol%)	Blood pressure (mm Hg)	Heart rate (min^{-1})
Control	86.1 ± 4.0	37.9 ± 1.7	7.40 ± .02	17.4 ± 1.0	84 ± 3.1	179 ± 9.5
Hypercarbia	108.9 ± 4.5†	59.9 ± 1.4†	7.27 ± .02†	17.2 ± 0.7	84 ± 3.9	184 ± 9.9

* Mean ± SE for $n = 7$ determinations.
† $P < 0.05$ using critical Bonferroni value of $t^* = 2.93$.

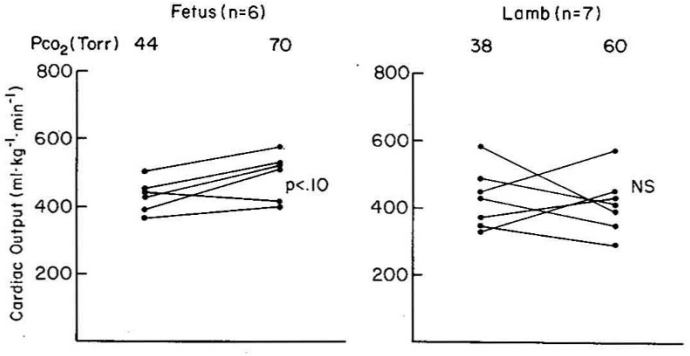

Fig. 1. Total cardiac output ($ml \cdot kg^{-1}\ min^{-1}$) with hypercarbia in the fetal and neonatal lamb. Each *pair* of *points* connected by a *line* represents an individual animal.

Table 3. *Organ blood flows: fetuses**

	Control	Hypercarbia
Cerebral cortex†	113 ± 13	200 ± 16
Cerebellum†	134 ± 15	263 ± 28
Brainstem†	156 ± 23	415 ± 46
Heart	137 ± 15	154 ± 14
Placenta	182 ± 14	182 ± 14
Carcass	21 ± 1	21 ± 2
Skin	22 ± 1	20 ± 2
Kidneys	192 ± 15	192 ± 13
Liver	2 ± 0.5	3 ± 0.4
Spleen	392 ± 43	296 ± 35
Stomach	52 ± 12	49 ± 8
Small bowel	113 ± 11	146 ± 13
Large bowel	47 ± 3	54 ± 6
Adrenals	271 ± 42	243 ± 49
Diaphragm†	18 ± 5	100 ± 27
Lungs†	112 ± 35	235 ± 38

* Mean ± SE for $n = 6$ determinations ($ml \cdot 100\ g^{-1}\ min^{-1}$).
† $P < 0.05$ using a critical Bonferroni value of $t^* = 3.20$.

Table 4. *Organ blood flows: lambs**

	Control	Hypercarbia
Cerebral cortex†	78 ± 6	196 ± 14
Cerebellum†	93 ± 6	229 ± 22
Brainstem†	74 ± 6	283 ± 24
Heart	170 ± 14	208 ± 16
Carcass	25 ± 3	25 ± 2
Skin	21 ± 2	19 ± 2
Kidneys	537 ± 65	400 ± 20
Liver	17 ± 8	12 ± 5
Spleen†	561 ± 50	346 ± 47
Stomach†	167 ± 42	107 ± 23
Small bowel	332 ± 31	273 ± 27
Large bowel	143 ± 20	126 ± 9
Adrenals	335 ± 49	362 ± 54
Diaphragm†	27 ± 2	180 ± 46
Lungs (bronchial)	73 ± 21	73 ± 26

* Mean ± SE for $n = 7$ determinations ($ml \cdot 100\ g^{-1}\ min^{-1}$).
† $P < 0.05$ using a critical Bonferroni value of $t^* = 3.19$.

Table 5. *Developmental comparison of circulatory changes with hypercarbia*

	Fetus	Lamb	Adult*
Pa_{CO_2} (mm Hg)†	26	22	22
Cardiac output ($ml \cdot kg^{-1}\ min^{-1}$)	→	→	→
Organ flows ($ml \cdot 100\ g^{-1}\ min^{-1}$)			
CNS	↑	↑	↑
Diaphragm	↑	↑	↑
Heart	→	→	→
Stomach	→	↓	Not measured
Spleen	→	↓	→
Pulmonary	↑	Not measured	Not measured

* Matalon *et al.* (21).
† Ranges studied: fetus (44–70 mm Hg), lamb (38–60 mm Hg), adult (36–58 mm Hg).

nificantly decreased (Table 4). There were no significant changes in flow to the remaining organs.

DISCUSSION

There are similarities but important differences as well in the distribution of cardiac output with hypercarbia among fetal, newborn, and adult sheep (Table 5). Complex interactions among a number of factors that may be influenced by development may be involved in the circulatory changes during respiratory acidosis. Individual vessels may dilate because of the local effects of CO_2. This has been shown experimentally in a variety of vascular beds including cerebral (20), mesenteric (7), coronary (9), renal (13), and limb (13, 29). On the other hand, hypercapnia provokes peripheral vasoconstriction via an effect both on the central nervous system (15) and peripheral chemoreceptors (27). Elevations in Pa_{CO_2} also increase respiration and stimulate the

pulmonary stretch receptors which induce skin, muscle, renal, and splanchnic vasodilation (12, 32). Finally, organ blood flow response to $Paco_2$ may be influenced by different functional stages in organ develoment.

These experiments were only descriptive. With that in mind, the ensuing discussion will consider possible explanations of the circulatory responses to CO_2 we observed. Specific studies designed to answer these questions will be necessary in order to investigate these possibilities.

In the lamb, we found significant redistribution of cardiac output. There were increases in flow to all CNS structures thought to be secondary to local vasodilation by CO_2 (20), and an increase in diaphragm flow secondary to the stimulation of breathing (19). The increases in CNS and diaphragm flows were qualitatively similar to those in our fetuses and Matalon's adults (21). These increases in flow were accompanied by significant decreases in splenic and stomach blood flows, as well as consistent (seven of seven animals) but not statistically significant decreases in small bowel and renal blood flows, perhaps due to the predominance of vasoconstrictive effects of CO_2 mediated by central vasomotor centers (15) and/or peripheral chemoreceptors (27). These decreases were not observed in the fetus, which could be due to immaturity of the fetal autonomic nervous system (5, 14, 34). However, at comparable increases in CO_2 in the adult sheep, renal, intestinal, and splenic flows were unchanged as well (21). Explanations unrelated to the autonomic nervous system may therefore be important. Baseline splenic and intestinal flows are considerably higher in the lamb than in the adult or fetus. This relative state of vasoconstriction in the fetus and adult may make these beds less responsive to chemoreceptor-induced vasoconstriction with hypercarbia than is the case in the lamb. Secondly, there are functional intestinal differences: the intestines are not functioning as a digestive organ in the fetus, the lamb is on a purely milk diet, and the adult is a ruminant. The importance of these differences on the response of their respective blood flows to hypercarbia needs to be investigated.

The most striking finding in the fetus was a large increase in pulmonary blood flow. This increase occurred in all six fetuses studied and averaged 110% of control (Fig. 2). There are several potential explanations for this finding including: local effects of $Paco_2$ or Pao_2 on the pulmonary vasculature, or the effects of the induction of fetal breathing on the pulmonary vasculature. Data from adults (21) and neonates (31) show no change or increased pulmonary vascular resistance during respiratory or metabolic acidosis. Studies in fetal sheep have failed to identify an independent effect of $Paco_2$ on pulmonary blood flow (25). However, the increase in fetal pulmonary flow could have been due to the rise in fetal Pao_2 that accompanied respiratory acidosis. Respiratory acidosis produces a rightward shift in the maternal oxyhemoglobin dissociation curve that would raise uterine vein and thus umbilical vein Po_2 (23). A similar shift in the fetal dissociation curve will raise umbilical vein Po_2 by a more complex mechanism discussed in detail by Meschia *et al.* (24). As a result, fetal Pao_2 in the abdominal aorta increased from 23 to 28 mm Hg. Changes in Pao_2 over this range have been shown to cause marked increases in pulmonary blood flow (22). One other factor also involved in the increase in pulmonary blood flow is suggested by the increase in diaphragm flow. Hypercapnia induces fetal breathing (6) and consequently an increase in blood flow to the diaphragm (26). Fetal breathing movements may also independently increase pulmonary blood flow (25).

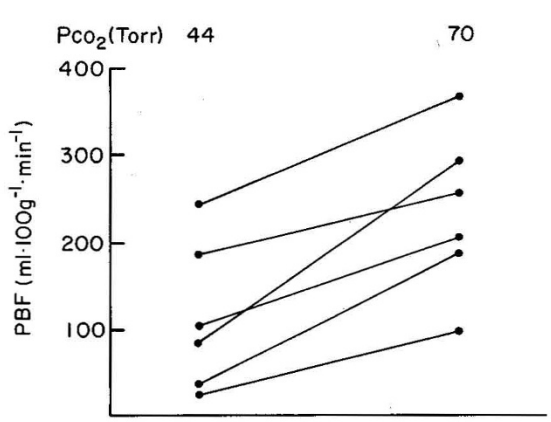

Fig. 2. Pulmonary blood flow (*PBF*; ml · 100 g^{-1} min^{-1}) with hypercarbia in the fetal lamb. Each *pair* of *points* connected by a *line* represents an individual animal.

The individual effects of the various influences on the fetal vascular response to hypercapnia are difficult to dissect. The "normal" fetal Pao_2 is quite low by postnatal standards. In adults, the combination of hypoxia and hypercapnia enhances peripheral chemoreceptor activity (11). However, unlike with the lamb, we have no evidence of chemoreceptor-induced vasoconstriction even in beds likely to show a chemoreflex-mediated decrease in flow (spleen and stomach). There are several possible explanations. The central vasomotor center and peripheral chemoreceptors might not respond to the degree of hypercapnia induced in our fetal studies or the autonomic effector system might not be fully developed. There is evidence from fetal lamb studies that carotid, but not aortic chemoreceptor sensitivity is suppressed until the time of birth (5, 14), and that fetal cardiovascular response to autonomic agonists increases during intrauterine and postnatal develoment (34). It is also possible that vasoconstrictive effects are present but counterbalanced by CO_2-induced local vasodilation.

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Diabetes in Pregnancy: Decreased Placental Blood Flow and Disturbed Fetal Development in the Rat

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Summary

Placental blood flow was measured with the aid of radioactive microspheres, in normal (N) and manifest diabetic (MD) rats, and related to fetal body growth and incidence of congenital malformations. The total blood flow in the placentae of the MD rats was decreased to about one-half of the normal flow on gestational days 20 and 22. The placentae of the MD offspring were enlarged, whereas the fetuses in this group were smaller than normal. Thus, the placental blood flow *per placental weight* was drastically decreased in the MD fetuses on both days 20 and 22. In contrast, the placental blood flow *per fetal weight* was not different in the N and MD groups on gestational day 20 whereas it was decreased in the MD offspring on gestational day 22. Placental blood flow in the malformed fetuses of the MD group did not differ significantly from that in the nonmalformed MD fetuses.

Abbreviations

N, normal control rat (nondiabetic)
N20 or N22, normal pregnant rat on gestational day 20 or 22
MD, manifest diabetic rat (serum glucose level exceeding 20 mmol/liter)
MD20 or MD22, pregnant manifest diabetic rat on gestational day 20 or 22

The etiology of altered fetal development defined as increased/decreased fetal weight, malformations, and an increased number of resorptions in the diabetic pregnancy is at present not clear (23). Disturbances in the transfer of nutrients from mother to fetus, reflecting altered placental function, may be of importance for the decreased somatic growth rate (17, 18). Besides, the magnitude of the placental blood flow determines the amount of nutrients available for transfer to the fetus (27). Therefore, placental blood flow may be relevant to fetal growth retardation (28). Decreased placental blood supply has been accomplished experimentally in rats subjected to uterine artery ligation (21) and maternal dietary restriction (29). The offspring of these rats show decreased fetal weights and increased number of intrauterine resorptions.

Although a number of estimations of placental blood flow in rodents have been reported (1, 2, 5, 7, 15, 16, 27, 29, 34), no studies of placental blood flow in diabetic rat pregnancy seem to have been published. There are, however, reports of altered placental morphology (26) and indirect evidences of changed vascular function in diabetic rat placenta (4) as well as decreased transfer of aminoisobutyric acid to fetuses of diabetic guinea pigs (30). Also, reduced uteroplacental blood flow as determined with placental scintigraphy has recently been demonstrated in human diabetic pregnancy (19).

The aim of the present study was to examine the relation