Hepatic Oxygen and Glucose Metabolism in the Fetal Lamb

RESPONSE TO HYPOXIA

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ABSTRACT Although the fetal liver is an active metabolic organ, its oxygen and glucose requirements have not previously been described. We measured hepatic blood flows and the oxygen and glucose differences across the liver in 12 late gestation fetal lambs in utero. Four animals were studied at least 1 wk postsurgically and again 2–5 d later to assess daily variations in hepatic blood flow and metabolism (group I). A second group of eight animals was studied 3–5 d postsurgically during a control period and during acute fetal hypoxia (group II). Under control conditions total hepatic blood flow averaged 400 ml/min per 100 g in both groups, and 75–80% was of umbilical origin. Liver blood flow and oxygen consumption were usually similar during repeated measurements, but in one animal varied considerably. During periods of normoxia, oxygen consumption for both the right and left lobes of liver was 4 ml/min per 100 g. Oxygen consumption of the whole liver accounted for 20% of total fetal oxygen consumption. This was achieved with oxygen extraction of 10–15%, so that hepatic venous blood was well oxygenated and provided an important source of oxygen for other fetal tissues. Under control conditions we could demonstrate no net hepatic uptake or release of glucose suggesting that the liver ultimately utilizes another carbon source to support its oxidative metabolism.

During acute hypoxia total liver blood flow and its umbilical venous contribution both fell by 20%. Blood flow to the right lobe of the liver fell twice as much as that to the left lobe. Hepatic oxygen consumption was linearly related to oxygen delivery during the control and hypoxic periods. Consequently, right hepatic oxygen uptake fell by 45% whereas left hepatic oxygen uptake was unchanged, suggesting a functional difference between the lobes. During hypoxia glucose was released from both liver lobes; 6 mg/min per 100 g for the right lobe and 9 mg/min per 100 g for the left lobe. Total hepatic release of glucose was estimated to nearly equal umbilical uptake, so that 45% of the glucose available to fetal tissues was of hepatic origin. We conclude that the fetal liver responds to acute hypoxia by reducing its own oxygen consumption and releasing glucose to facilitate anaerobic metabolism.

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INTRODUCTION

We have reported previously that liver blood flow in the fetal lamb is in excess of 400 ml/min per 100 g (1). Because this large blood flow is primarily derived from umbilical venous return (1, 2), the delivery of placentally acquired oxygen and energy substrates to the liver is also large (3). The fetal liver is engaged in many synthetic metabolic processes (4–6) and, although it might be expected on the basis of these observations that the energy requirements of the fetal liver are large, hepatic uptake of oxygen and energy substrates has not been measured directly. Based on studies of tissue slices in vitro Carlyle in 1945 estimated that liver oxygen consumption ($\dot{V}O_2$) accounted for 20% of total fetal $\dot{V}O_2$ (7). These measurements have not been confirmed in vivo.

When the fetus is subjected to acute hypoxia, it has the ability to reduce its $\dot{V}O_2$ and, although oxygen delivery ($\dot{D}O_2$) to the brain, heart, and adrenals is maintained (8), oxygen supply to other fetal tissues is

greatly reduced. Under this circumstance there is an increased need for anaerobic energy substrates. Liver glycogen content rises rapidly after 130-d gestation (4) and fetal distress has been shown to stimulate glycogen degradation and raise circulating glucose concentrations in fetal lambs (9). However, the quantitative importance of glucose release from the liver in vivo has not been examined.

We have previously reported methods for measuring umbilical venous, portal venous, and hepatic arterial blood flows to the liver, and for sampling blood from these vessels (1). Recently we have developed a technique for obtaining samples of hepatic venous blood (10), making it possible to measure directly hepatic consumption of oxygen and energy substrates. Using these techniques we have examined hepatic $\dot{V}O_2$ and glucose consumption ($\dot{V}_G$) during periods of adequate oxygenation and during acute hypoxia in unanesthetized fetal lambs in utero.

GLOSSARY

C period	control period
$cpm_{(IVC)}A$	activity of IVC injected isotope appearing in organ A
$cpm_{(PV)}A$	activity of PV injected isotope appearing in organ A
$cpm_{(UV)}A$	activity of UV injected isotope appearing in organ A
$\dot{D}_G$	glucose delivery
$\dot{D}O_2$	oxygen delivery
FA*	femoral artery
H period	hypoxemic period
HA*	hepatic artery
HV	hepatic vein
IVC	inferior vena cava
LHV	left hepatic vein
PV	portal vein
$\dot{Q}_{(HA)}$ liver	blood flow to liver from hepatic artery
$\dot{Q}_{PV}$	total portal venous blood flow
$\dot{Q}_{(PV)}$ liver	blood flow to liver from portal vein
$\dot{Q}_{ref}$	reference sample withdrawal rate
$\dot{Q}_{Total}$ rt liver	total blood flow to the right liver lobe
$\dot{Q}_{UV}$	total umbilical venous blood flow
$\dot{Q}_{(UV)}$ liver	blood flow to liver from umbilical vein
$\dot{Q}_{UV}$ rt liver	flow to the right liver lobe derived from UV
RHV	right hepatic vein
UV	umbilical vein
$\dot{V}_G$	glucose uptake or release
$\dot{V}O_2$	oxygen consumption

* HA and FA bloods are both derived from descending aorta.

METHODS

We studied 12 fetuses divided into two groups. Four fetuses of gestational age 127–133 d were studied on two occasions 6–14 d postoperatively to assess daily variations in hepatic blood flow, $\dot{V}O_2$ and V_G for the right liver lobe (group I). Eight fetuses of gestational age 116–123 d were studied 3–5 d postoperatively during a control period and during acute hypoxia (group II). Mean fetal weights were 3.48±0.69 kg for group I and 2.34±0.53 kg for group II.

Surgical preparation

Anesthesia of the lower body of the ewe was achieved by epidural injection of 2 ml of 2% tetracaine-HCl (Pontocaine, Breon Laboratories, New York). Pentobarbital was administered intravenously in doses of 120 mg as needed to augment anesthesia. Polyvinyl catheters (2.3-mm o.d., 1.3-mm i.d.) were advanced to the maternal aorta and inferior vena cava (IVC) via a pedal artery and vein. The ewe's abdomen was opened in the midline and, through a small hysterotomy, the fetal hind limbs were exposed one at a time. Polyvinyl catheters (1.8-mm o.d., 1.0-mm i.d.) were inserted into the pedal artery and vein of each hind limb and advanced to the descending aorta and IVC. A 3.5F multiple side-hole catheter was then introduced into a distal cotyledonary tributary of the umbilical vein (UV) and advanced so that its tip lay in one of the main UV 8–10 cm from the umbilical ring. Before closing this uterine incision, we placed a multiple side-hole polyvinyl catheter into the amniotic sac and secured it to the uterine wall. Through a second uterine incision, the right lower quadrant of the fetal abdomen was exposed. A 2–3-cm incision was made in the anterior abdominal wall and several loops of small bowel were extracted. Through a tributary usually peripheral to the venous arcade of the ileum, a polyvinyl catheter (0.90-mm o.d., 0.038-mm i.d.) was threaded 5–6 cm so that its tip lay in the PV just below the liver. We had previously confirmed that, in fetuses of this gestational age, catheters advanced this distance do not enter the portal sinus. After closing the fetal abdominal incision, we repositioned the uterine incision over the right eighth rib of the fetus. A right thoracotomy was performed and the eighth rib was resected to allow visualization of the IVC as it passed through the diaphragm. We have been able to selectively cannulate the right (RHV) and left hepatic veins (LHV) through the IVC. To do this, a purse-string suture was placed in the posterior wall of the IVC and the vein was punctured with a No. 11 scalpel blade. Through this puncture a 3.5F multiple side-hole catheter was advanced 3 cm across the IVC and into the RHV or LHV. The catheter was secured by tightening the purse-string suture. The catheter position could be verified by comparing blood oxygen saturations in the IVC, UV, and the hepatic veins (HV) (10). Both HV contain blood with a saturation between those of umbilical venous and caval blood. The saturation of left hepatic venous blood is higher than that of right hepatic venous blood because desaturated portal venous blood is distributed entirely to the right lobe (1), thereby lowering its oxygen saturation relative to the left lobe.

All fetuses in group I had right hepatic venous catheters, whereas in group II, three fetuses had right hepatic venous catheters, three had left hepatic venous catheters, and two of the larger fetuses had catheters in both right and left HV. We did not routinely catheterize both HV in the smaller fetuses for fear of constricting the IVC by placing two purse-string sutures.

The fetal chest was then closed. The uterine incision was sutured after the instillation of 1 million U of penicillin and 400 mg of kanamycin. Lost amniotic fluid was replaced with warm normal saline. All catheters were exteriorized to the left flank of the ewe; they were filled with heparin solution, plugged, and protected by a cloth pouch sewn to the skin.

All fetal and maternal catheters were kept patent by daily flushes with normal saline after which the dead space was

filled with heparin (1,000 IU/ml). Intraamniotic antibiotics (1 million U of penicillin and 400 mg kanamycin) were also given daily. The ewe was allowed free access to alfalfa pellets and water.

Experimental

On the day of study, the ewe was placed in a metabolic cage with free access to food and water. All fetal and maternal catheters were flushed with normal saline, and continuous recording of fetal arterial and amniotic pressures and heart rate was begun. After a steady base-line heart rate and blood pressure were observed, control measurements were made. We began by determining organ blood flows using the radioactive microsphere method. 15-μm microspheres labeled with isotopes selected from ^{125}I, ^{153}Gd, ^{57}Co, ^{51}Cr, ^{113}Sn, ^{85}Sr, ^{46}Sc, and ^{95}Nb were prepared as previously described (12). Injections of three different labeled microspheres were made simultaneously into IVC, umbilical venous, and portal venous catheters for measurement of placental, portal, and hepatic blood flows (see Appendix for calculations). A reference sample was withdrawn at a rate of 4–8 ml/min from the descending aorta from just before microsphere injection until 1 min after each catheter was flushed. The actual rate was determined by weighing the syringe before and after withdrawal. Immediately after the end of the reference withdrawal, 1-ml samples were collected from descending aorta, UV, PV, HV, and IVC for blood glucose and 0.8-ml samples for blood gas and oxygen saturation measurements. The glucose samples were deproteinized immediately with $Ba(OH)_2$ and $ZnSO_4$, spun, and frozen for later analysis by the glucose oxidase method. We have shown previously that freezing and thawing after 2–3 wk storage does not alter measured glucose concentrations. All glucose samples were prepared and analyzed in duplicate and the difference between paired samples was usually 1–2% and always <5%. Blood gas samples were analyzed for PO_2, PCO_2, and pH using a Radiometer blood gas analyzer (London Co., Copenhagen). Oxygen saturation and hemoglobin values were measured in duplicate with a Radiometer hemoximeter (OSM_2). Oxygen saturation measurements on duplicate samples were always within 0.5%, and hemoglobin measurements were always within 0.2 g/dl of each other. Oxygen content was calculated from these measurements. The volume of blood removed from the fetus was replaced by donor fetal lamb blood. At this point the catheters of group I fetuses were flushed and closed and the study was repeated 2–5 d later.

For group II animals, after a 30-min equilibration period, we then produced fetal hypoxia by administering a gas mixture of 10% oxygen in nitrogen to the ewe through a loosely fitting plastic bag placed over her head. The onset of fetal hypoxia was heralded by a fall in fetal heart rate after 2–3 min. We waited 9–15 min (mean = 11 min) for heart rate to stabilize before checking fetal aortic PO_2 and repeating microsphere injections and blood sampling as during the control period. The total duration of hypoxia was <30 min in each case.

The ewe was killed with intravenous sodium pentobarbital and KCl, and the uterus and its contents were removed. Each fetus was weighed and dissected carefully to verify the position of each catheter. Fetal organs were removed, weighed, and placed in formalin before preparation for microsphere counting.

Microsphere counting and calculations. The liver was divided into right and left lobes along a line joining the midpoint of the UV as it enters the liver and the midpoint of the IVC at the superior margin of the liver. The caudate lobe was removed from the inferior surface of the right lobe and counted separately. The mean liver weight was 122.7±26.9 for group I fetuses and 82.2±15.2 g for group II. Radioactivity of the gastrointestinal tract from the esophagus at the level of the diaphragm to the middle of the rectum, and of the pancreas, was measured together and that of the spleen was counted separately.

All fetal tissues were carbonized and placed in counting vials in standardized fashion as previously described (11). Samples were counted in a well-type gamma scintillation counter and analyzed by a multichannel pulse height analyzer. The specific activity of each isotope within a sample was calculated using a least squares analysis that minimizes the squared error between the observed spectrum and linear combinations of the known spectrum for each isotope. Three regions of interest near the spectral peak of each isotope were used. A X^2 value for each sample was calculated and used to assess the adequacy of sample preparation and to screen for zero and gain changes during counting. The statistical error associated with the calculation of specific activites was <2% for each isotope. In practice, the activity of each isotope can be estimated to ±5 (±1 SD)% in the presence of the other seven isotopes. This latter error is somewhat larger because it includes random error introduced by differences in sample density and distribution of the isotope within the sample (12).

The calculation of umbilical, portal, and hepatic blood flows and estimates of the errors associated with each are described in detail in the Appendix. Umbilical uptake of oxygen and glucose were calculated as the product of umbilical blood flow and the arteriovenous oxygen and glucose differences. $\dot{D}O_2$ to the liver was calculated as the sum of the products of oxygen content and blood flow from HA, PV, and UV. Hepatic $\dot{V}O_2$ was calculated for the right or left lobe by subtracting the product of total hepatic blood flow to that lobe and hepatic venous oxygen content from hepatic $\dot{D}O_2$. Hepatic $\dot{V}_G$ was calculated in analogous fashion. Hepatic $\dot{V}_G$ may be positive, indicating hepatic uptake of glucose, or negative, indicating hepatic release of glucose.

Hepatic $\dot{V}O_2$ and $\dot{V}_G$ could be calculated only for the lobe from which a hepatic venous sample was obtained. All group I animals had right hepatic venous catheters. For group II animals, we estimated total liver $\dot{V}O_2$ and $\dot{V}_G$ by assuming values of $\dot{V}O_2$/100 g and $\dot{V}_G$/100 g for the lobe from which a hepatic venous sample was not obtained, based on the actual measurements of $\dot{V}O_2$ and $\dot{V}_G$ for that lobe.

All data are presented as the mean followed by lower and upper quartiles in parentheses (25th and 75th percentiles). We have chosen this method of presentation because some of the smaller flows and the oxygen content data appear to be drawn from a skewed population to which parametric statistics may not be applied. For those data that are normally distributed the standard deviation may be obtained by dividing the interquartile distance by 1.35. Statistical comparisons were carried out using the Mann-Whitney U statistic for unpaired data and the Wilcoxon signed rank test for paired data (13). Regression analysis was carried out by standard methods. As a measure of the day-to-day variability of data from group I animals, we calculated the difference between paired measurements as a percentage of the mean of the two values (i.e., $2(X_1 - X_2)/X_1 + X_2$) and then averaged the percentage differences.

RESULTS

Fetal descending aortic pH, PO_2, and PCO_2 for both group I and group II animals were within the normal

TABLE I

Fetal Descending Aortic Blood Gases, and Mean Arterial Pressures, and Heart Rates for Group I and Group II during the Control (C) and Hypoxemic (H) Period (mean and lower and upper quartiles). Arterial Pressure and Heart Rate Were Not Recorded at the Time of Study in Group I Animals, but Were in the Same Range as Group II Animals, When Recorded

	Group I	Group II		P	
	Control	Control	Hypoxemia	I vs. II	C vs. H
PO_2 (*torr*)	20 (19, 21)	21 (19, 23)	11 (9, 13)	NS	<0.01
PCO_2 (*torr*)	47 (46, 48)	42 (41, 44)	38 (35, 40)	NS	<0.05
pH (*units*)	7.35 (7.34, 7.36)	7.38 (7.36, 7.39)	7.39 (7.36, 7.41)	NS	NS
Mean arterial pressure (*torr*)		40 (38, 43)	51 (46, 62)		<0.05
Heart rate (*per min*)		180 (162, 192)	144 (125, 160)		<0.005

range for lambs of this gestational age (14), and there were no significant differences in PO_2 or pH between the two groups but the PCO_2 in group I was slightly higher (Table I). Mean arterial blood pressure and heart rate were also similar to those recorded from fetuses of this gestational age in utero. Maternal hypoxia resulted in a significant decrease in fetal descending aortic PO_2 from 21 (19, 23) to 11 (9, 13) mmHg; pH did not change, but PCO_2 fell slightly as a result of maternal hyperventilation. Mean arterial pressure increased and heart rate fell to levels similar to those previously reported for fetal lambs exposed to hypoxia of this severity and duration (3, 14).

Umbilical blood flow was similar for groups I and II under control conditions (Table II). There were also no significant differences in fetal $\dot{V}O_2$, $\dot{V}_G$, or the umbilical arteriovenous oxygen and glucose differences between the two groups. The glucose/oxygen quotient

TABLE II

Umbilical Placental Blood Flow, Umbilical Venoarterial Differences for Oxygen and Glucose, and Fetal Placental Uptake of Oxygen and Glucose Are Shown for Group I and During the C and H periods for Group II.

	Group I	Group II		P	
	Control	Control	Hypoxemia	I vs. II	C vs. H
Umbilical blood flow (*ml/min/kg*)	206 (186, 222)	224 (194, 241)	209 (171, 244)	NS	NS
Umbilical venoarterial oxygen difference (*ml/dl*)	3.8 (3.5, 4.1)	3.1 (2.3, 3.8)	2.3 (1.7, 3.0)	NS	<0.01
Oxygen uptake across placenta (*ml/min/kg*)	7.7 (6.6, 8.4)	6.8 (6.1, 7.4)	4.5 (3.6, 5.3)	NS	<0.01
Umbilical venoarterial glucose difference (*mg/dl*)	2.1 (1.7, 2.7)	1.6 (0.8, 2.2)	1.2 (0.4, 1.8)	NS	NS
Glucose uptake across placenta (*mg/min/kg*)	5.0 (3.3, 7.8)	3.4 (2.1, 4.7)	2.4 (0.9, 4.1)	NS	NS

Numbers shown are mean, and in parentheses, lower and upper quartiles. Group I $n = 8$, group II $n = 8$.

was 0.44 (0.35, 0.51) for group I animals and 0.38 (0.25, 0.47) for group II. During fetal hypoxia the umbilical arteriovenous oxygen difference fell, while umbilical blood flow did not change significantly. Consequently fetal $\dot{V}O_2$ fell by 35%. The umbilical arteriovenous glucose difference and $\dot{V}_G$ were unchanged by hypoxia. The glucose/oxygen quotient was 0.37 (0.13, 0.56) during hypoxia.

Hepatic blood flow and its components are shown in Table III. Total hepatic blood flow was similar for group I and group II animals during normoxia when normalized for liver weight: 408 (356, 460) vs. 396 (315, 515) ml/min per 100 g liver. Umbilical venous blood comprised 82% of the total for group I animals and 73% of total flow for group II. There were no significant differences in umbilical flow between groups or between right and left lobes in either group when data were normalized for weight. Portal venous blood contributed 14% of total hepatic flow in group I and 22% in group II, and in both groups it was distributed entirely to the right and caudate lobes. Although actual portal venous flow to liver was greater in group I, when normalized for weight total portal flow to liver was significantly less in group I than in group II ($P < 0.05$). Hepatic arterial flow accounted for the remaining 5% of hepatic blood flow in both groups.

Some representative right hepatic flow data from group I are included in Table IV. The mean percent difference between paired measures of umbilical flow to the right lobe was 25%, and 30% for portal venous and total flow to the right lobe. Similar differences were found for flows to the left lobe, so that the mean differences were for total umbilical flow, 25%; for total portal venous flow, 30%; and for total hepatic blood flow, 23%.

Fetal hypoxia produced a significant fall in total hepatic blood flow to 304 (208, 396) ml/min per 100 g ($P < 0.01$). This was accounted for primarily by a fall in umbilical venous blood flow to the whole liver from 285 (197, 386) to 224 (162, 297) ml/min per 100 g ($P < 0.01$). Umbilical venous flow to the right lobe fell by 25% ($P < 0.01$); however, umbilical venous flow to the left lobe did not change significantly. Portal venous flow to the liver also fell significantly ($P < 0.05$) and, as during the control period, it was confined to the right and caudate lobes.

Table V lists the oxygen contents in each fetal vessel and the oxygen differences across the liver. Group II data have been further divided into two subgroups depending upon which HV was catheterized. Data from the two group II animals with catheters in both HV have been included in both subgroups. There were no differences between oxygen contents in group I and group II animals during normoxia. In particular, we noted that hepatic venous oxygen content had stabilized by the third postoperative day and it remained stable for the duration of our studies (up to 2 wk).

Both right and left hepatic venous blood oxygen contents were below that in umbilical venous blood and above those in descending aortic and portal venous blood. These findings indicate that portal venous and hepatic arterial blood may acquire oxygen from umbilical venous blood in their transit through hepatic sinusoids and venous channels. We have previously reported that right hepatic venous oxygen saturation was below that in the left hepatic vein (10). Although mean right hepatic venous oxygen content in this group of studies was lower than that in the left, the difference was not statistically significant. Right hepatic venous oxygen content was also lower than that in the left hepatic vein in the two animals in which both veins were catheterized.

With hypoxia, there was a significant reduction in the oxygen content within each fetal vessel. Despite this, oxygen differences between umbilical venous and both hepatic venous bloods were maintained. The HA to HV and PV to RHV oxygen differences were narrowed, but these changes were not statistically significant.

Hepatic $\dot{D}O_2$, its components, and $\dot{V}O_2$ for each group are illustrated in Fig. 1. Total $\dot{D}O_2$ to the right lobe was similar for group I and group II animals: 34.1 (28.2, 39.9) as compared with 39.0 (33.9, 50.0) ml/min per 100 g. Umbilical venous blood contributed 88% of the total for group I and 83% of the total for group II animals. Total $\dot{D}O_2$ to the left lobe was 26.9 (20.2, 34.6) ml/min per 100 g; this was significantly less than that to the right lobe in group II animals ($P<0.05$). Umbilical venous $\dot{D}O_2$ to the left lobe was not significantly different from that to the right lobe, and it contributed 99% of total $\dot{D}O_2$ to the left lobe.

Hepatic $\dot{V}O_2$ was calculated by subtracting the quantity of oxygen in blood leaving the liver in the HV from the quantity delivered to the liver. The values thus obtained for the right lobe were 3.9 (3.2, 4.5) and 3.9 (3.3, 4.4) ml/min per 100 g for groups I and II, respectively, and 4.4 (2.7, 5.6) ml/min per 100 g for the left lobe. For group II fetuses we estimated that total hepatic $\dot{V}O_2$ was 19% of total fetal $\dot{V}O_2$.

$\dot{D}O_2$, the UV to HV oxygen differences, and hepatic $\dot{V}O_2$ for each animal in group I are shown in Table IV. Not surprisingly these data show the same variability as hepatic blood flow. In general the UV to HV oxygen difference more closely reflected $\dot{V}O_2$ than did $\dot{D}O_2$.

During acute hypoxia both total $\dot{D}O_2$ and umbilical venous $\dot{D}O_2$ to the right lobe fell by 60% ($P < 0.01$). Consequently, right hepatic $\dot{V}O_2$ fell by 40% to 2.4 (2.0, 3.1) ml/min per 100 g ($P < 0.05$). $\dot{D}O_2$ to the left lobe fell less than that to the right lobe and left hepatic

TABLE III

Blood Flow to Individual Lobes of the Liver, and to the Whole Liver, Derived from the HA, UV, and PV Is Shown during C and H Periods. Actual Blood Flows and Blood Flows Related to Liver Weight Are Presented

		Actual blood flows (ml)			
		HA	UV	PV	TOTAL
Right lobe					
Group I		7	218	57	287
		(5, 11)	(196, 239)	(33, 77)	(257, 335)
Group II	C	14	128	51	189
		(1, 20)	(67, 177)	(31, 73)	(145, 238)
	H	16	89	44	148
		(1, 30)	(50, 118)	(28, 48)	(113, 167)
Left lobe					
Group I		3	172	0	174
		(2, 6)	(141, 202)	(0, 1)	(146, 203)
Group II	C	1	78	0	80
		(0, 1)	(51, 95)	(0, 0)	(52, 96)
	H	3	70	0	72
		(1, 3)	(52, 85)	(0, 1)	(55, 91)
Caudate					
Group I		3	25	19	47
		(2, 6)	(14, 32)	(9, 26)	(29, 58)
Group II	C	1	15	19	35
		(0, 1)	(6, 21)	(5, 31)	(21, 37)
	H	1	11	8	20
		(0, 2)	(5, 15)	(3, 12)	(12, 32)
Whole liver					
Group I		8	415	76	499
		(6, 17)	(347, 462)	(45, 104)	(423, 563)
Group II	C	14	214	65	294
		(2, 22)	(126, 312)	(45, 83)	(208, 379)
	H	19	167	50	236
		(2, 24)	(104, 236)	(34, 68)	(172, 307)
		Blood flows per 100 g liver weight			
Right lobe					
Group I		12	327	81	426
		(9, 14)	(288, 320)	(54, 105)	(347, 460)
Group II	C	30	289	126	442
		(2, 57)	(169, 412)	(70, 148)	(354, 569)
	H	42	217	105	362
		(3, 77)	(120, 275)	(67, 143)	(282, 416)
Left lobe					
Group I		9	366	1	372
		(7, 11)	(297, 455)	(0, 2)	(302, 464)

TABLE III (*Continued*)

		Actual blood flows (ml)			
		HA	UV	PV	TOTAL
		Blood flows per 100 g liver weight			
Group II	C	6	286	1	294
		(0, 7)	(183, 386)	(0, 0, 1)	(197, 391)
	H	10	250	1	265
		(1, 10)	(205, 306)	(0, 0, 1)	(208, 327)
Caudate					
Group I		38	293	213	506
		(18, 62)	(203, 397)	(112, 300)	(345, 655)
Group II	C	10	281	370	719
		(2, 19)	(102, 488)	(119, 791)	(324, 1120)
	H	15	171	162	382
		(3, 23)	(73, 236)	(71, 225)	(185, 586)
Total liver					
Group I		9	337	62	408
		(11, 15)	(287, 366)	(46, 77)	(356, 460)
Group II	C	18	285	91	396
		(2, 34)	(197, 386)	(75, 101)	(315, 515)
	H	26	224	66	304
		(3, 56)	(162, 297)	(58, 82)	(208, 396)

Numbers shown are mean, and in parentheses, upper and lower quartiles.

TABLE IV

Measurements Made in the Fetal Lambs in Group I on Two Different Days are Shown. $\dot{Q}_{UV}$ rt Liver—Flow to the Right Liver Lobe Derived from the UV. $\dot{Q}_{Total}$ Rt Liver—Total Blood Flow to the Right Liver Lobe; $\dot{D}O_2$, $\dot{V}O_2$, $\dot{D}_G$, and $\dot{V}_G$[*]

	Animal No.							
	1		2		3		4	
Gestational age	127	132	129	131	125	127	129	133
Umbilical blood flow (*ml/min/kg*)	193	190	182	291	250	194	193	155
$\dot{Q}_{UV}$ rt liver (*ml/min/100 g*)	237	297	280	551	306	317	323	296
$\dot{Q}_{Total}$ rt liver (*ml/min/100 g*)	353	414	333	613	416	514	427	342
$\dot{D}O_2$ rt liver (*ml/min/100 g*)	28.1	40.0	25.9	52.7	29.0	28.3	29.2	39.7
UV-RHV $\dot{D}O_2$ (*ml/dl*)	3.7	2.3	1.4	2.0	2.1	1.9	1.9	1.7
VO_2 rt liver (*ml/min/100 g*)	6.1	3.8	2.0	5.0	3.5	4.0	3.2	3.2
$\dot{D}_G$ rt liver (*mg/min/100 g*)	55.0	72.0	48.6	90.7	57.2	47.6	70.9	62.7
$\dot{V}_G$ rt liver (*mg/min/100 g*)	3.4	0.8	−1.8	0.2	11.4	15.5	−3.5	−0.3

[*] A positive number indicates uptake, whereas a negative number indicates release of glucose.

TABLE V

The Blood Oxygen Contents Measured in Various Fetal Vessels during the C and H Periods, as well as Oxygen Content Differences between the Vessels Shown

	O_2 contents (ml/dl)				
Right lobe	FA	UV	PV	RHV	IVC
Group I	5.3 (3.9, 6.3)	9.1 (7.6, 10.6)	3.8 (2.5, 5.1)	7.0 (5.6, 7.6)	3.0 (2.3, 3.5)
Group II					
Control	5.9 (4.7, 6.9)	9.0 (7.4, 10.6)	4.3 (2.8, 5.2)	6.9 (5.7, 8.0)	3.9 (2.8, 4.7)
Hypoxia	2.9 (2.2, 3.6)	5.3 (4.2, 6.2)	1.3 (0.5, 2.2)	3.3 (2.6, 4.2)	1.5 (0.9, 1.9)
I vs. II	NS	NS	NS	NS	NS
C vs. H	<0.01	<0.01	<0.05	<0.01	<0.01
Left lobe	FA	UV	LHV	IVC	
Group II					
Control	6.9 (5.5, 9.0)	10.2 (8.5, 11.8)	8.5 (7.2, 9.9)	4.7 (3.2, 6.2)	
Hypoxia	3.5 (2.5, 4.1)	5.7 (4.7, 7.2)	3.9 (3.0, 4.4)	1.8 (1.0, 2.9)	
	O_2 content differences				
	FA-RHV	UV-RHV	PV-RHV	FA-LHV	UV-LHV
Group I					
Control	−1.8 (−2.1, −1.2)	2.1 (1.8, 2.2)	−3.1 (−3.4, −2.5)		
Group II					
Control	−1.0 (−1.9,−0.5)	2.0 (1.6, 2.5)	−2.8 (−3.9, −2.0)	−1.6 (−2.3, −1.2)	1.7 (1.2, 2.3)
Hypoxia	−0.4 (−0.7, −0.2)	1.9 (1.8, 2.8)	−2.0 (−2.4, −1.4)	−1.2 (−1.5, −0.8)	1.8 (0.9, 2.5)
I vs. II	NS	NS	NS		
C vs. H	NS	NS	NS	NS	NS

Numbers shown are mean, and in parentheses, upper and lower quartiles.

$\dot{V}O_2$ did not change. The net fall in hepatic $\dot{V}O_2$ was proportional to that of the whole fetus so that the liver still accounted for 20% of total fetal $\dot{V}O_2$.

Calculated oxygen extraction for the right lobe was 12.0 (8.5, 13.0) for group I, and 10.4 (7.7, 12.2) for group II. Left lobe oxygen extraction was 15.8 (12.8, 18.5). During hypoxia right lobe oxygen extraction increased slightly to 17.1 (12.8, 24.0) while left lobe oxygen extraction doubled to 32.3 (17.5, 44.0). Neither change was statistically significant.

Hepatic $\dot{V}O_2$ was linearly related to $\dot{D}O_2$ (Fig. 2). There was no difference between regression lines for right and left lobes, or between control and hypoxic states. Hence the regression shown is that for all data points.

Fetal glucose concentrations and the glucose differences across the liver for each group are shown in Table VI. Group I fetuses showed a progressive fall in blood glucose concentrations in the first 5 postoperative d, after which time blood glucose concentrations stabilized or rose slightly. Hence, group I animals had significantly lower blood glucose concentrations than group II animals. Despite the lower glucose concentrations in these animals, the UV to RHV glucose difference was wider and the other glucose differences across the liver were less negative in group I than in

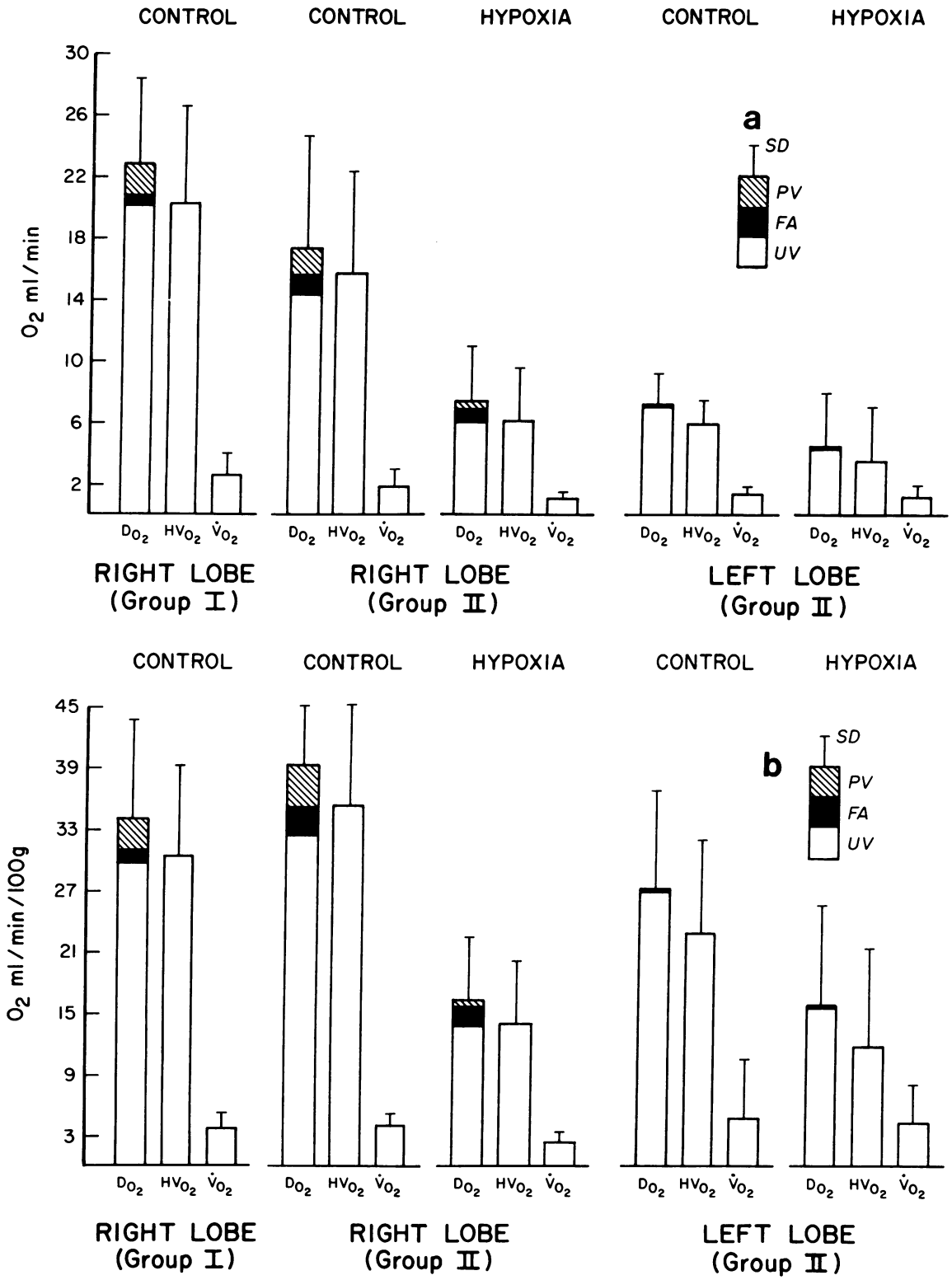


FIGURE 1 Hepatic $\dot{D}O_2$ and $\dot{V}O_2$ for group I and group II during C and H periods. Values are mean±1 SD. DO_2 is divided into components from UV, PV, and FA. Oxygen leaving the liver in hepatic vein ($H\dot{V}O_2$) was subtracted from $\dot{D}O_2$ to obtain $\dot{V}O_2$. Actual values are shown in Fig. 1a; Fig. 1b shows data normalized for liver weight. Group I $n = 8$, group II $n = 5$ for each lobe.

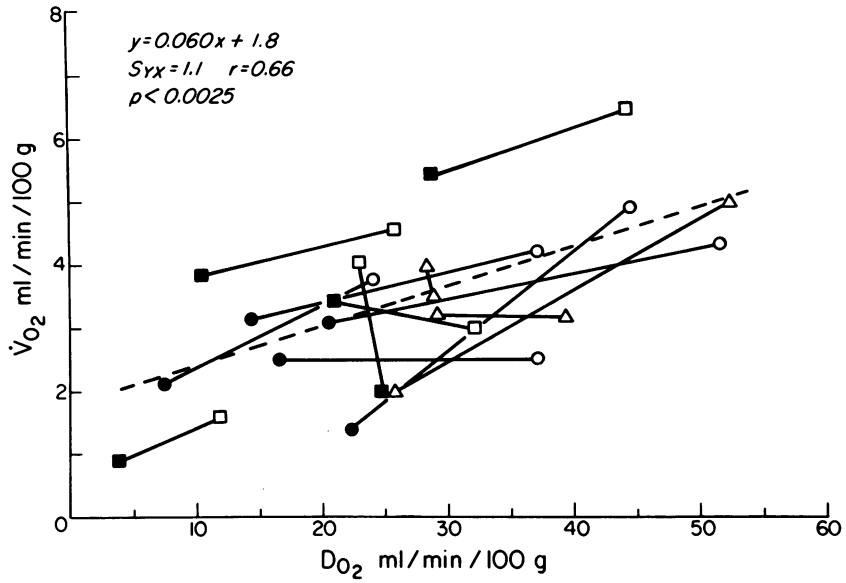


FIGURE 2 Hepatic $\dot{V}O_2$ as a function of $\dot{D}O_2$ to the liver. Group I animals, right lobe, triangles. Group II animals, left lobe, squares; right lobe, circles. Control, open symbols; hypoxia, filled symbols. The regression includes all data shown.

group II. There were no statistical differences between the two groups. Within group II during control there was no significant difference in glucose concentrations of right and left hepatic venous blood.

Hepatic $\dot{V}_G$ was calculated in analogous fashion to $\dot{V}O_2$ and is illustrated in Fig. 3. For the right lobe, $\dot{V}_G$ was 3.2 (−1.1, 7.4) mg/min per 100 g for group I and −1.7 (−3.1, 0.1) mg/min per 100 g for group II. This difference was not statistically significant. The relatively large value of $\dot{V}_G$ for group I and its large standard deviation reflect animal No. 3 in which $\dot{V}_G$ was 11.4 and 15.5 mg/min per 100 g on two occasions (Table IV). This animal was not distinguishable from others by its gestational age, blood oxygen or glucose concentrations, or hepatic blood flow and its distribution. $\dot{V}_G$ for the left lobe during control was −0.7 (−1.9, 1.5) and the 95% confidence limits of $\dot{V}_G$ for all control groups included zero.

With the onset of hypoxia, both right hepatic venous and left hepatic venous glucose concentrations rose above that in the UV, indicating release of glucose from both lobes. $\dot{V}_G$ was −2.4 (−2.8, −1.3) mg/min for the right lobe and −2.5 (−2.8, −1.3) mg/min for the left lobe. Both changes were significant ($P < 0.01$). When these data were normalized for the weight of each lobe, the left lobe was releasing 50% more glucose than the right (−8.9 [−5.0, −11.1] vs. −5.8 [−7.6, −2.7] mg/min per 100 g). Calculated total hepatic $\dot{V}_G$ during hypoxia was −4.8±0.8 mg/min, a value equal to 83% of umbilical $\dot{V}_G$. Hepatic $\dot{V}_G$ was not related to umbilical $\dot{V}_G$ or $\dot{V}O_2$; descending aortic or umbilical venous PO_2, or glucose concentration; or to delivery of oxygen or glucose to the liver.

DISCUSSION

We have studied hepatic oxygen and glucose metabolism in two groups of chronically catheterized fetal lambs. Group I animals were studied twice from 5 to 13 d postoperatively to assess day-to-day variation in hepatic blood flow and metabolism. These fetuses all had normal blood gases but blood glucose concentrations were slightly lower than in the group II animals. Despite this they consumed both oxygen and glucose at rates similar to those reported in the literature (15) and hence had normal glucose/oxygen quotients. This is unlike the observations reported for 24–72-h fasts in which both fetal blood glucose concentrations and the glucose/oxygen quotient fell dramatically (16, 17). Longer periods of hypoglycemia have not been well studied, and it would appear that these fetuses adapted to more prolonged hypoglycemia. Group II fetuses were studied from the third to the fifth postoperative day and during normoxia they had normal blood gases and normal blood glucose concentrations. There was no difference in umbilical oxygen or glucose uptake between the two groups.

The magnitude and origins of hepatic blood flow in these studies were similar to those reported from this laboratory (1) and others (2). There was considerable

TABLE VI

Blood Glucose Contents Measured in Various Fetal Vessels during the C and H Periods, as well as Glucose Differences between the Vessels Shown

Glucose (mg/dl)	FA	UV	PV	RHV	IVC	FA	UV	LHV	IVC
Group I									
Control	14.2 (12.9, 15.4)	16.3 (15.5, 17.1)	13.1 (12.4, 13.9)	14.8 (14.2, 16.2)					
Group II									
Control	19.7 (16.3, 24.4)	21.3 (18.1, 25.4)	18.7 (16.0, 23.0)	21.1 (17.9, 25.8)	18.9 (15.7, 22.4)	19.9 (16.3, 24.7)	21.8 (19.3, 25.5)	21.8 (19.5, 25.4)	17.7 (14.7, 22.2)
Hypoxia	22.0 (18.8, 24.3)	23.4 (21.1, 25.0)	20.0 (17.2, 23.3)	24.1 (21.5, 26.5)	18.3 (16.6, 19.4)	20.8 (17.3, 26.7)	22.0 (16.8, 23.7)	26.5 (21.4, 32.7)	16.4 (21.4, 32.7)
I vs. II	<0.02	<0.02	<0.01	<0.01					
C vs. H	NS	NS	NS	NS	NS	NS	NS	NS	NS

Glucose difference (mg/dl)	FA-RHV	UV-RHV	PV-RHV	FA-LHV	UV-LHV
Group I					
Control	−0.6 (−2.5, 1.0)	1.5 (0.2, 2.7)	−1.7 (−3.2, 1.5)		
Group II					
Control	−1.4 (−2.2, −0.7)	0.3 (−0.2, 0.5)	−2.5 (−3.0, −1.9)	−1.9 (−3.0, −0.7)	−0.1 (−0.5, 0.6)
Hypoxia	−2.1 (−2.4, −1.6)	−0.9 (−1.5, −0.2)	−4.0 (−4.9, −2.8)	−5.7 (−8.1, −3.3)	−4.5 (−6.7, −1.9)
I vs. II	NS	NS	NS		
C vs. H	NS	<0.05	NS	<0.05	<0.02

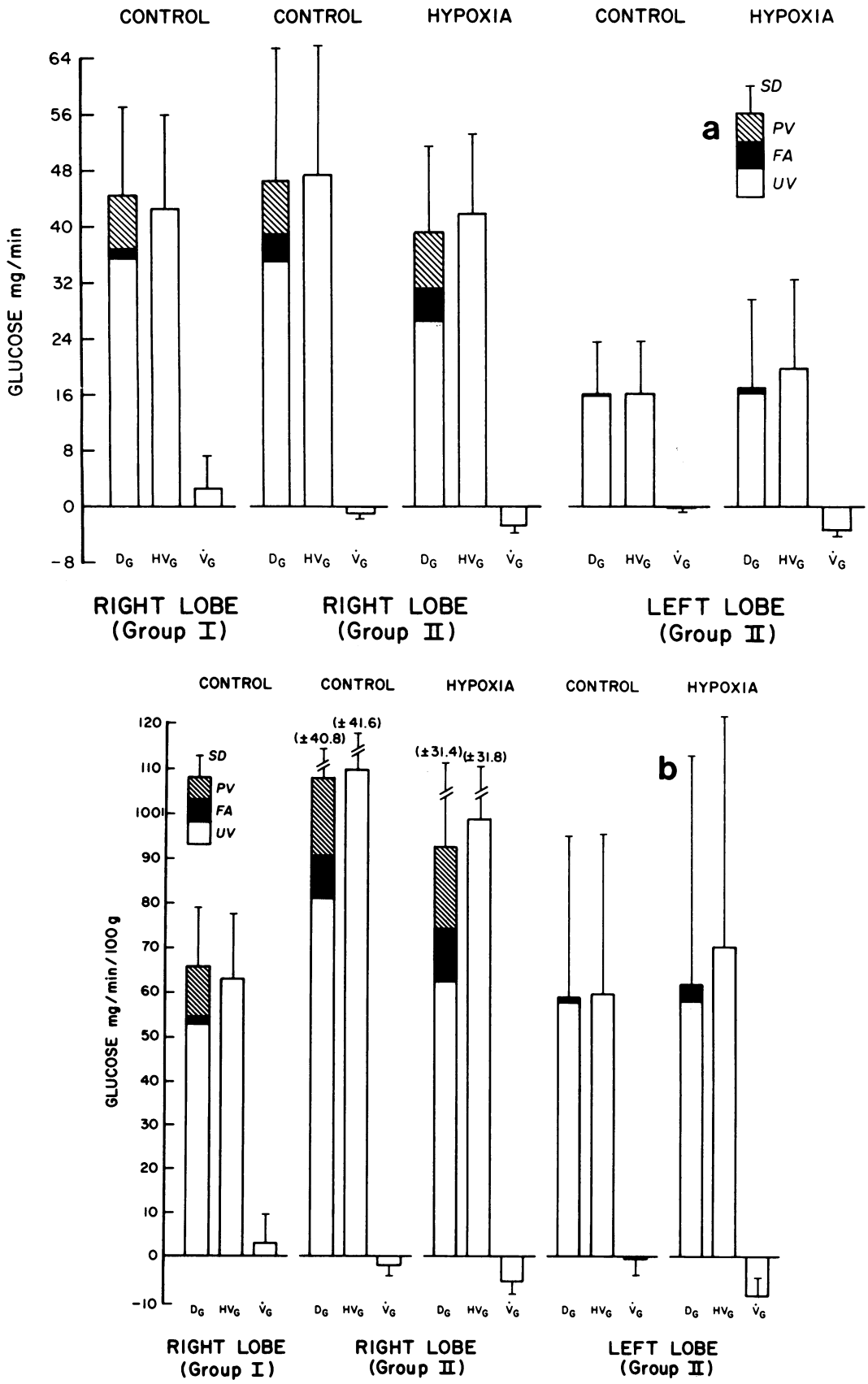
Numbers shown are mean, and in parentheses, upper and lower quartiles.

variability in hepatic blood flow and its components, but not more than in prior studies. There was generally less variability of flows from any individual animal in group I, but mean differences between paired flows were 25–30%. This variation is more than would be expected from the errors inherent to the measurement of hepatic blood flow by the microsphere method (Appendix). Analysis of variance of the group I animal data gave similar estimates of variance, within and between animals, of total hepatic blood flow and of each of its components. Hence it appears that there is normally considerable variation in hepatic blood flow not only between animals, but from day-to-day in the same animal.

Well-oxygenated umbilical venous blood comprised the major fraction of hepatic blood flow in these studies, and as a result $\dot{D}O_2$ to the liver was large. Hepatic $\dot{V}O_2$ was linearly related to $\dot{D}O_2$ and so $\dot{V}O_2$ also was large (~4 ml/min per 100 g for both lobes). This is equal to the $\dot{V}O_2$ of the fetal brain (18), and is about half that of the fetal heart (19). We estimate that the fetal liver is responsible for 20% of total fetal $\dot{V}O_2$.

Although the oxygen requirements of the specific metabolic processes responsible for this large $\dot{V}O_2$ have not been delineated, it is clear that the fetal liver is engaged in many of the same synthetic functions as that of the adult in addition to serving as the primary site of hematopoiesis. Because the relatively large oxygen demands of the fetal liver are met by very high blood flow and little oxygen extraction, hepatic venous blood from both lobes is well oxygenated. Further, because hepatic venous return is nearly equal in magnitude to umbilical venous return across the ductus venosus, it follows that hepatic venous blood is an important source of oxygen for other fetal tissues.

During fetal hypoxia, there was a significant reduction in total and umbilical venous blood flow to the liver. Interestingly, the decrement was not shared equally by the two lobes, the reduction in flow to the right lobe being nearly twice that to the left. Edelstone


CONTROL
CONTROL
HYPOXIA
CONTROL
HYPOXIA
GLUCOSE mg/min
64
56
48
40
32
24
16
8
0
-8
SD
PV
FA
UV
a
DG HVG V̇G
RIGHT LOBE (Group I)
RIGHT LOBE (Group II)
LEFT LOBE (Group II)
CONTROL
CONTROL
HYPOXIA
CONTROL
HYPOXIA
GLUCOSE mg/min/100 g
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
(±40.8)
(±41.6)
(±31.4)
(±31.8)
b
RIGHT LOBE (Group I)
RIGHT LOBE (Group II)
LEFT LOBE (Group II)

et al. (30) have demonstrated that when umbilical blood flow is reduced by balloon occlusion of the descending aorta, there is also a greater reduction in umbilical venous flow to the right lobe than to the left. These findings suggest that the two lobes may independently modify their vascular resistance in response to stressful stimuli. The interplay of vascular reflexes, circulating vasoactive substances, and local factors in producing changes in hepatic vascular resistance has not been examined.

The reduction in umbilical blood flow to the liver superimposed upon a 40% reduction in umbilical venous oxygen content produced dramatic reductions in $\dot{D}O_2$ to the liver. Again this effect was most pronounced for the right lobe where $\dot{D}O_2$ fell by >50%. The reduction in $\dot{D}O_2$ to the left lobe was smaller and not statistically significant, although the standard deviation associated with these measurements was large. $\dot{V}O_2$ by both lobes was linearly related to $\dot{D}O_2$, so it is not surprising that right lobe $\dot{V}O_2$ fell significantly while that of the left lobe was relatively well maintained. These observations raise the question whether functional differences exist between the right and left lobes of the fetal liver. Histologic asymmetry of the liver has been noted in stillborn human infants (21) but similar studies of fetal ovine liver have not been reported. Further, it is unclear whether the reduction in right hepatic $\dot{V}O_2$ reflects a compensatory reduction in oxygen demand (which might effectively spare oxygen for other fetal tissues) or whether the reduction reflects tissue hypoxia within the right lobe. It has been shown in infants who died with birth asphyxia that the right lobe is ultimately more susceptible to anoxic injury (22). It should be noted that during hypoxia the right lobe of the liver is still perfused at a higher PO_2 than are other fetal organs because the oxygen content of right hepatic venous blood remains above that of descending aortic blood. Indeed, the $\dot{D}O_2$ of 16 ml/min per 100 g to the right lobe during hypoxia is somewhat higher than that seen by the fetal brain and heart, under conditions of normal oxygenation. Hence it seems unlikely that the reduction in right lobe $\dot{V}O_2$ is secondary to tissue hypoxia.

In this study right and left lobe $\dot{V}_G$ were not statistically different from zero during normoxia, although a positive value for $\dot{V}_G$ was obtained for some animals in group I. The finding that there is no appreciable uptake of glucose by the liver during periods of adequate oxygenation confirms the inference of previous investigators (15). The fetal liver lacks glucokinase, so phosphorylation of glucose must be catalyzed by the slower hexokinase reaction. Barnes et al. (4) have estimated the rate of glycogen accumulation to be 5 mg/g liver per d (or 0.3 mg/min per 100 g) after 125-d gestation; this is below the limit of detection of our method.

The finding that there is no net uptake of glucose by the liver also suggests that the liver must ultimately use a carbon source other than glucose to support its oxidative metabolism. It is well established that in unstressed fetal lambs, lactate (23, 24), and amino acids (5, 25) together may account for 50% of total fetal $\dot{V}O_2$. These substrates, like O_2 and glucose, are delivered to the liver in greater quantity than to any other organ. Utilization of these substrates by the liver for oxidation or for glucose and glycogen synthesis might effectively spare glucose for organs such as the brain that are obligate or preferential users of glucose (26).

During hypoxia, hepatic glucose release was 2.4 mg/min and 2.5 mg/min for right and left lobes, respectively. Total hepatic $\dot{V}_G$ was calculated to be 4.8 mg/min, while umbilical uptake was 5.9 mg/min. Because glucose is not released to a significant extent from any other fetal tissues, 45% of the glucose available to fetal tissues was of hepatic origin during acute hypoxia.

Although our studies do not indicate the source of glucose released from the liver, the likelihood is that hepatic glycogenolysis is responsible. Devos and Hers (27) have shown that turnover of hepatic glycogen is extremely slow in near-term rats under normal conditions, but that glycogen is quickly mobilized under the stress of maternal anesthesia. A rise in plasma glucose and a fall in liver glycogen content have also been reported during asphyxia in fetal lambs (9). The glucose released could have arisen from gluconeogenesis, but there is much conflict about whether gluconeogenesis occurs during fetal life (16, 28). Without additional data, we can only assume that hepatic glycogen is the major source of glucose released.

The precise stimulus for glucose release during hypoxia has not been defined. Plasma concentrations of both epinephrine and norepinephrine are elevated (29), and physiologic doses of these agents have been shown to produce elevated circulating glucose concentrations and a reduced hepatic glycogen content in fetal lambs (30). In the fetal lamb, physiologic doses of catecholamines increased circulating immunoreactive glucagon activity and suppressed immunoreactive

FIGURE 3 Hepatic glucose delivery and uptake for group I and for group II during C and H periods. Values are mean±1 SD. Glucose delivery (D_G) is divided into components coming from UV, PV, and FA. Glucose leaving the liver in the HV ($H\dot{V}_G$) was subtracted from $\dot{D}_G$ to obtain $\dot{V}_G$. Positive values reflect hepatic uptake while negative values reflect hepatic release of glucose. Actual values are shown in Fig. 3a; Fig. 3b shows data normalized for liver weight. Group I n = 8, group II n = 5 for each lobe.

insulin, whereas blood glucose rose significantly (31). In mature animals, catecholamines appear to produce glycogenolysis by interacting with an alpha adrenergic receptor on the hepatocyte surface, and the intracellular mechanism thus activated acts independently of the adenyl cyclase pathway by which glucagon exerts its effect (32). Although the effects of catecholamines and glucagon on fetal hepatocytes have not been studied directly, it has been suggested that adrenergic modulation of glucagon, insulin, and glucose concentrations is mature by 110 d in the fetal lamb (31).

Recently, a number of other peptide hormones, including angiotensin II, arginine vasopressin, and vasoactive intestinal peptide, have been shown to stimulate hepatic glycogenolysis in vitro and in vivo (23). Of these, only vasopressin has been shown to be released during hypoxia in amounts that are sufficient to produce glycogenolysis (33). Finally, both oxygen and glucose have been shown to have direct effects on hepatic glycogenolysis (27). Our data do not allow us to identify the stimulus for glucose release.

The fate of the glucose released by the liver during hypoxia is not known, but will depend on the distribution of hepatic venous blood to fetal organs and their rates of glucose utilization. We have shown that the liver is important in providing a large proportion of substrate for fetal metabolism during acute hypoxia. In our studies the duration of hypoxia was short; it is important to determine whether the liver can supply glucose for longer periods of fetal stress.

APPENDIX

For all abdominal organs except liver

$$\dot{Q}\ \text{organ} = \dot{Q}_{\text{ref}} \times \frac{\text{cpm}_{(\text{IVC})}\ \text{organ}}{\text{cpm}_{(\text{IVC})}\ \text{ref}}. \quad (1)$$

Hepatic arterial flow to each liver lobe was calculated from the IVC injection using Eq. 1. Because hepatic arterial flow is small, relatively few microspheres (~400) are deposited in the liver via this route and we estimate an error of <10% for this measurement.

When Eq. 1 is applied to the placenta it yields total umbilical venous blood flow ($\dot{Q}_{UV}$). Eq. 1 is equally applicable to UV-injected microspheres (11), and we have averaged the values of $\dot{Q}_{UV}$ and total portal venous blood flow ($\dot{Q}_{PV}$) obtained with paired IVC and UV injections. In our study the mean difference between paired estimates of placental blood flow was 6.0 (1.2, 9.3). Blood flows to gut, spleen, and pancreas were summed to give $\dot{Q}_{PV}$, and a similar error 7.0 (2.6, 10.3) was found for paired measurements of portal venous flow.

The distribution of portal venous and umbilical venous flows to liver were calculated using Eqs. 2 and 3.

$$\dot{Q}_{(\text{PV})}\ \text{liver} = \dot{Q}_{\text{PV}} \times \frac{\text{cpm}_{(\text{PV})}\ \text{liver}}{\text{cpm}_{(\text{PV})}\ \text{total}} \quad (2)$$

$$\dot{Q}_{(\text{UV})}\ \text{liver} = \frac{\text{cpm}_{(\text{UV})}\ \text{liver} - \left[\text{cpm}_{(\text{IVC})}\ \text{liver} \times \frac{\text{cpm}_{(\text{UV})}\ \text{ref}}{\text{cpm}_{(\text{IVC})}\ \text{ref}}\right]}{\text{cpm}_{(\text{UV})}\ \text{total}}. \quad (3)$$

Eq. 3 corrects for the fact that some UV-injected microspheres will cross the ductus venosus and be distributed to the liver via the HA.

Eqs. 2 and 3 are based on the assumption that microspheres injected into the UV and PV are adequately mixed within these vessels, so that their distribution within the liver accurately reflects that of portal venous and umbilical venous blood. Edelstone et al. (20) have verified this assumption using a preparation very similar to that used in this study. In their study they found that paired injections into two umbilical venous tributaries were distributed similarly.

The ratio of numbers of microspheres trapped in the liver from paired injections had a SD of 0.10 (CV of 11%). For paired portal venous injections the ratio of trapped microspheres had a SD of 13%. When combined with the independent errors associated with measurement of total umbilical venous and total portal venous blood flow, errors of up to 12 and 15% for umbilical venous and portal venous flows to liver are obtained.

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