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Effects of reducing uterine blood flow on fetal blood flow distribution and oxygen delivery

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Abstract

We examined the effect of graded reduction in uterine blood flow on distribution of cardiac output and oxygen delivery to fetal organs and venous blood flow patterns in 9 fetal sheep using the radionuclide-labeled microsphere technique. We reduced uterine blood flow in two steps, decreasing fetal oxygen delivery to 70% and 50% of normal, and compared the results with those from a similar study from our laboratory on graded umbilical cord compression. With 50% reduction in fetal oxygen delivery, blood flow and the fraction of the cardiac output distributed to the brain, heart, and adrenal gland increased and that to the lungs, carcass, skin, and scalp decreased. Oxygen delivery to the brain and myocardium was maintained, while that to the adrenal doubled, and that to the brain stem increased transiently. The decrease in oxygen delivery to both carcass and lower body segment correlated linearly with oxygen consumption ($P<0.001$). The proportion of umbilical venous blood passing through the ductus venosus increased from 44.6% to 53% ($P<0.05$). The preferential distribution of ductus venosus blood flow through the foramen ovale to the heart and brain increased, but that to the upper carcass decreased so that ductus venosus-derived blood flow to the upper body did not change. Hence, the oxygen delivered to the brain from the ductus venosus was maintained, and that to the heart increased 54% even though ductus venosus-derived oxygen delivery to the upper body fell 34%. Abdominal inferior vena caval blood flow and its contribution to cardiac output decreased, but the proportion of the abdominal inferior vena caval blood distributed through the foramen ovale also increased from 23.0 to 30.9%. However, the actual amount of inferior vena caval blood passing through the foramen ovale did not change. There was a 70% fall in oxygen delivery to the upper body segment from the inferior vena cava. A greater portion of superior vena caval blood was also shunted through the foramen ovale to the upper body, but the actual amounts of blood and oxygen delivered to the upper body from this source were small. Thus, graded reduction of uterine blood flow causes a redistribution of fetal oxygen delivery and of venous flow patterns, which is clearly different from that observed previously during graded umbilical cord occlusion.

Introduction

Reduced oxygen supply is the usual cause of fetal distress. Experimentally, fetal oxygen deficiency can be produced by maternal hypoxemia (Cohn, Sacks, Heymann & Rudolph 1974), by reducing umbilical blood flow (Itskovitz, LaGamma & Rudolph 1987), or by restricting uterine blood flow (Wilkening & Meschia 1983). These conditions, which result in fetal hypoxemia and asphyxia and largely determine fetal morbidity and mortality in human pregnancy, each have their clinical counterpart. Thus, maternal lung diseases would reduce arterial oxygen content; cord compression during labor would reduce umbilical blood flow and hence oxygen delivery to the fetus; and prolonged severe uterine contractions in the second stage of labor would restrict uterine blood flow by increasing uterine vascular resistance. A number of studies have been performed in unanesthetized fetal sheep to assess fetal cardiovascular responses to maternal hypoxemia (Bristow, Rudolph, Itskovitz & Barnes 1983; Cohn *et al.*, 1974; Peeters, Sheldon, Jones, Makowski & Meschia 1979) and reduction in umbilical blood flow (Itskovitz, LaGamma & Rudolph 1983; Itskovitz *et al.*, 1987). Effects of reduction in uterine blood flow have been studied acutely by Jensen, Hohmann & Künzel (1987), Yaffe, Parer, Block & Llanos (1987), and by Wilkening & Meschia (1983).

In this study we examined the effect of graded reduction in uterine blood flow on the distribution of cardiac output, organ blood flow, and oxygen delivery to fetal organs as well as on flow patterns of venous

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return. To compare the results of the present study with those from a similar study from our laboratory on graded umbilical cord compression, we reduced uterine blood flow in two steps to achieve a decrease in fetal oxygen delivery to 70% and 50% of normal.

Materials and methods

Animal preparation

Nine pregnant ewes near term (123-129 days gestation; term is ~147 days) were anesthetized with 2 ml of 1% tetracaine HCl (Pontocaine HCl, Breon Laboratories Inc., New York, NY, USA) injected into the epidural space at the lower spine. Polyvinyl catheters (OD 2.3 mm, ID 1.3 mm) were inserted into branches of a maternal femoral artery and vein and advanced to the descending aorta and inferior vena cava, respectively. Ketamine HCl, 50 mg, was given intravenously every 10-15 min to maintain sedation. The ewe's abdomen was opened in the midline, and a snare was placed around the common segment of the uterine artery so that uterine blood flow could be controlled. Through a small uterine incision, the fetal hindlimbs were exposed. Using local anesthesia with 0.5% lidocaine HCl, polyvinyl catheters (OD 1.2 mm, ID 0.8 mm) were inserted via the pedal artery and vein of each hind leg into the descending aorta and inferior vena cava, respectively. The incision was extended and two 3.5 F multiple side-hole catheters were advanced via distal cotyledonary tributaries of the umbilical vein to one of the main umbilical veins. A catheter was placed in the amniotic cavity, and the uterine incision was closed. A second uterine incision was made over the fetal neck to insert catheters via a common carotid artery and external jugular vein into the brachiocephalic trunk and superior vena cava. Through the same incision, which was repositioned to expose the parietal and occipital regions of the fetal head without exteriorizing it, a pair of stainless steel wire electrodes were placed biparietally on the fetal dura to record the electrocortical activity (Clewlow, Dawes, Johnston & Walker 1983). In addition, in four fetuses the superior sagittal sinus was catheterized using a specially prepared catheter needle assembly. This was inserted at the junction of the sagittal and lambdoid sutures. Amniotic fluid was replaced with warm saline (0.9%, w/v), which contained 1 million units of penicillin G and 400 mg of kanamycin, and the incision was closed. All catheters were filled with heparin (1,000 IU/ml) and plugged. All catheters and electrodes and the snare were passed subcutaneously to the ewe's flank, where they were exteriorized and protected by a pouch sewn to the skin. On the day of operation and each day thereafter, the ewe received 2 million units of penicillin G and 800 mg of kanamycin sulfate, half intravenously and half into the amniotic cavity.

Experimental protocol

Nine experiments, one on each fetus (weight 2.9 ± 0.7 kg), were conducted *in utero* on the third or fourth day after the operation while the ewe stood quietly in a study cage with access to food and water. Fetal and maternal catheters were flushed with warm saline (0.9% NaCl, 39C), and a continuous recording was begun of fetal descending aortic, inferior vena caval, umbilical venous, and intrauterine pressures, and heart rate and electrocortical activity. After approximately two hours of control recording, in which episodes of high- and low-voltage electrocortical activity were observed, blood samples were obtained during low-voltage activity from the descending and ascending aorta, umbilical vein, inferior vena cava, and superior vena cava to measure blood gases, oxygen saturation of hemoglobin, and acid-base balance. To determine the blood flow to fetal organs, the distribution of cardiac output, and the distribution of venous blood returning to the heart via the inferior vena cava, superior vena cava, and ductus venosus, three batches of differently labeled microspheres (selected from ^{153}Gd, ^{57}Co, ^{114}In, ^{51}Cr, ^{113}Sn, ^{85}Sr, ^{95}Nb, ^{65}Zn, or ^{54}Mn; 3-M Company, MI, USA; New England Nuclear, Boston, MA, USA) were injected simultaneously into the inferior vena cava, superior vena cava, and umbilical vein during low-voltage electrocortical activity while reference samples were withdrawn (at a rate of 4 ml/min for 75 s) from the ascending and descending aortic catheters. The volume of blood removed was replaced with warm fetal or maternal blood immediately after sampling.

Uterine blood flow was then gradually reduced by constricting the snare around the common uterine artery until fetal descending aortic oxygen saturation decreased to approximately 50% of the control value (Step 1). When heart rate and arterial blood pressure were stable, both blood sampling and microsphere injections were repeated (17 ± 5 min after starting to reduce uterine blood flow). Thereafter, to achieve a decrease in oxygen saturation to approximately 30% of the control value, uterine blood flow was further reduced (Step 2), and when heart rate and arterial blood pressure were stable again, blood sampling and microsphere injections were repeated (at 18 ± 8 min after Step 1). The snare was then released and blood samples were collected 30 and 60 min after recovery. At the end of the study the ewe was given a lethal dose of sodium pentobarbital and potassium chloride intravenously, and the fetus was perfused with 200 ml of formalin (15%, w/v). The uterus and its contents were removed, weighed, and prepared for radionuclide counting (Heymann, Payne, Hoffman & Rudolph, 1977). Correct placement of the catheters was verified.

Measurements and calculations

Descending aortic, inferior vena caval, umbilical venous, and intrauterine pressures were measured by Statham P23Db pressure transducers (Statham Instruments, Oxnard, CA, USA). Heart rate was monitored continuously with a cardiotachometer triggered

by the arterial blood pressure. The electrocortical activity was amplified (differential, high-gain amplifier with a band width [-6dB] of 1-300 Hz and an input noise of 1.8 μV) and filtered (3-30 Hz). All variables were recorded on a Beckman direct writing oscillograph (Beckman Instruments, Inc., Palo Alto, CA, USA). Amniotic fluid pressure was used as zero reference for fetal vascular pressures.

Blood gases and pH were measured in an automatic blood gas analyzer (model 168, Corning Glass Works, Medfield, MA, USA), and base excess was calculated. Hemoglobin concentration and oxygen saturation of hemoglobin were measured photometrically (Hemoximeter model OSM 2, Radiometer, Copenhagen, Denmark) in duplicate. Oxygen content of the blood was calculated according to the formula: oxygen content [ml/dl] = (hemoglobin [g/dl] x 1.34 x oxygen saturation of hemoglobin [%]) / 100; dissolved oxygen was considered negligible.

All fetal tissues, excluding lungs, carcass, and placenta, were carbonized and placed in counting vials as described previously (Heymann *et al.*, 1977). The intestines were separated from the mesentery, opened, and cleared of contents. Paired organs (lungs and kidneys) were counted separately, as were the right and left sides of the cerebrum. No preferential streaming of microspheres to either side of these organs was found, so complete mixing of the microspheres was assumed. In spite of ligation of one carotid artery, the distribution of blood flow to the right and left sides of the cerebrum was identical at control (84.0 ± 31.2 vs. 83.5 ± 27.9 ml/min x 100 g), and at Step 1 (159.0 ± 33.0 vs. 159.2 ± 47.7) and Step 2 of reduced uterine blood flow (170.9 ± 49.4 vs. 168.5 ± 61.1).

Samples were counted in a well-type gamma scintillation counter and analyzed by a multichannel (1024) pulse height analyzer (Norland, Fort Atkinson, WI, USA). The count rate of each individual isotope within a sample was calculated from a least-squares analysis; to control for errors due to zero and gain changes during counting, three regions of interest near the major photopeak of each isotope were chosen (Baer, Payne, Verrier, Vlahakes, Molodowitch, Uhlig & Hoffman 1984).

Fetal cardiac output, blood flow to the various organs, umbilical-placental blood flow, abdominal inferior vena caval flow, and superior vena caval blood flow were calculated from counts of the inferior vena cava injected nuclide recovered in fetal organs and placenta, from counts in the appropriate reference samples, and from the withdrawal rate of the reference sample. Pulmonary blood flow was derived from the counts of the nuclide injected into the superior vena cava and inferior vena cava as described previously (Heymann *et al.*, 1977; Rudolph & Heymann 1967).

To determine the distribution of abdominal inferior vena caval and superior venal caval flows, we calculated the distribution of microspheres injected into the inferior vena cava and those injected into the superior vena cava by dividing the counts of the individual organs by the total counts of fetus and placenta.

The methods for computing the distribution of umbilical venous blood to the liver and the ductus venosus and the distribution of ductus venosus blood flow to fetal organs have been described in detail (Edelstone & Rudolph 1979; Edelstone, Rudolph & Heymann 1978; Itskovitz, Goetzman & Rudolph 1982; Reuss & Rudolph 1980). Briefly, the portion of counts from microspheres injected into the umbilical vein that was trapped in the liver represented the fraction of umbilical venous blood to the liver. Similarly, the counts of microspheres injected into the umbilical vein that appeared in the fetal body and placenta represented the proportion of umbilical venous blood that passed through the ductus venosus. Actual blood flows to a given organ derived from ductus venosus and abdominal inferior vena cava and superior vena cava were calculated by multiplying the proportion of the total counts from venous-injected microspheres that were recovered in that organ by the blood flow through ductus venosus and inferior vena caval or superior vena caval flows.

Total hepatic blood flow was calculated by summing the contribution of umbilical venous blood to the liver, portal venous blood flow (the sum of blood flow to gastrointestinal tract and spleen), and hepatic arterial blood flow (Bristow *et al.*, 1983; Edelstone *et al.*, 1978; Edelstone, Rudolph & Heymann 1980; Itskovitz *et al.*, 1982). Total blood flow to the right and left lobes of the liver as well as the blood flows to subsections of each lobe were also calculated. The liver was divided into right and left lobes along a line joining the midpoint of the umbilical vein as it enters the liver and the midpoint of the inferior vena cava at the superior margin of the liver. The distribution of portal venous blood in the liver was not measured; based on previous observations before and during reduction of umbilical blood flow, hypoxemia, and hemorrhage, an almost exclusive distribution of portal venous blood flow to the right lobe of the liver was assumed (Bristow *et al.*, 1983; Edelstone *et al.*, 1978).

Total oxygen delivery to fetal organs was calculated as the product of organ blood flow and oxygen content of the blood in the vessel supplying the organ. Fractional oxygen delivery to fetal organs was calculated as the product of the fractional organ blood flow derived from ductus venosus and abdominal inferior vena cava and superior vena cava and oxygen contents in the blood in each of these veins. Pulmonary oxygen delivery was determined by summing the fractional delivery from each of the three venous returns to the lungs. Total hepatic oxygen delivery was calculated as the sum of oxygen delivered to the liver via umbilical venous, portal venous, and hepatic arterial blood flow. Because portal venous oxygen content was not measured, inferior vena caval oxygen content was used to estimate the amount of oxygen that was delivered by the portal venous blood to the liver (Bristow *et al.*, 1983).

The contribution of ductus venosus and abdominal inferior and superior vena caval blood to the total organ oxygen delivery was also determined. For example, the amount of oxygen delivered to the brain by ductus venosus blood equals the product of ductus venosus-derived blood flow to brain and ductus venosus oxygen content.

The oxygen consumptions ($\dot{V}O_2$) of the upper, lower, and total body of the fetus, of the upper and lower carcass, and of the brain were calculated. Also, oxygen extraction was calculated.

The vascular resistance within a given organ was calculated as the ratio of mean arterial minus venous blood pressure to the blood flow to that organ. The vascular resistance of the upper and lower body was calculated as the ratio of mean aortic minus inferior vena caval blood pressure to the total blood flow to the upper and lower body, respectively.

Data are expressed as means ± SD; they were analyzed statistically by the paired t-test. Because more than one comparison was made, a Bonferroni correction was performed to obtain the proper P-values (Miller 1966).

Results

The effects of graded reduction of uterine blood flow on fetal heart rate and blood pressure are shown in Table 1. During the first step (Step 1) of the reduction in uterine blood flow, which reduced hemoglobin oxygen saturation in descending aortic blood to 53% of control (i.e., from 58 ± 2% to 31 ± 2% oxygen saturation, range 23-40%), fetal heart rate decreased and mean aortic, umbilical venous, and inferior vena caval pressures increased. The average blood pressure difference across the placenta (33 mmHg) did not change, whereas that across the liver and ductus venosus increased (from 8 to 12 torr).

During Step 2 of blood flow reduction, which reduced oxygen saturation to 43% of control (i.e., to 25 ± 3% oxygen saturation, range 14-40%), fetal heart rate decreased further and aortic blood pressure increased further, while both umbilical venous and inferior vena caval blood pressures did not change. Thus, the average blood pressure difference across the placenta increased to 37 torr, whereas that across the liver and ductus venosus did not change.

After 30 and 60 min recovery, mean aortic, umbilical venous, and inferior vena caval blood pressures gradually returned towards normal, but heart rate was higher than in the control period. During the reduction of uterine blood flow, all animals had low-voltage electrocortical activity during Step 2, and all but one animal showed low-voltage activity during Step 1 reduction.

Fetal blood gases, oxygen content, pH, and base excess

Table 1 lists the blood gases, oxygen content, hemoglobin concentration, pH, and base excess in each fetal vessel. Graded reduction of uterine blood flow resulted in a progressive fall in PO_2, oxygen saturation, and oxygen content in blood obtained from each fetal vessel. Hemoglobin concentration increased. There was a progressive increase in PCO_2 and fall in pH. Although base deficit tended to increase, the changes were significant only in umbilical venous and inferior vena caval blood.

The oxygen content difference across the placenta (umbilical venous-descending aortic) did not change significantly during Step 1 reduction of uterine blood flow, but fell significantly during Step 2 (from 3.0 ± 0.9 to 1.7 ± 0.9 ml/dl, $P<0.001$). Interestingly, the arteriovenous oxygen difference across the upper body (ascending aorta-superior vena cava) decreased from 2.32 to 0.89 ml/dl, but that across the lower body (descending aorta-abdominal inferior vena cava) did not change significantly (1.98 to 1.77 ml/dl). There was also a decrease in the difference in oxygen content between ascending and descending aortic blood from 0.93 to 0.45 ml/dl.

After 30 and 60 min recovery, all variables tended to normalize, though pH and base excess were still significantly different from control. Also, umbilical venous and aortic oxygen saturations had not yet returned to control values.

Fetal cardiac output, organ blood flow, vascular resistance, oxygen consumption, and oxygen delivery

Although combined ventricular output fell slightly during Step 2 of uterine blood flow reduction, the change was not statistically significant (Table 2A). Umbilical-placental blood flow was maintained, but the proportion of the cardiac output distributed to the placenta increased. Blood flow, as well as the proportion of cardiac output received, increased to the brain, heart, and adrenal gland. Interestingly, blood flow to the myocardium increased further during Step 2 of uterine blood flow reduction, whereas flow to the brain and adrenals showed no further change.

Blood flow to the lungs, as well as the proportion of cardiac output, decreased with reduction in uterine blood flow. Although blood flows to the kidneys and small bowel decreased, the changes did not reach statistical significance. The flows to the carcass of both the upper and lower body showed a marked decrease, and specifically, skin blood flow fell dramatically. Although mean muscle blood flow fell, the change was not statistically significant.

The changes in blood flow to the brain and spinal cord were determined in 34 different parts of the cerebrum, cerebellum, diencephalon, midbrain, medulla, and the upper and lower spinal cord enlargements, as well as the hypophysis and choroid plexus. During the control period, blood flow was lowest in the cerebrum and highest in the midbrain and medulla. During graded uterine blood flow reduction, blood flow to all parts of the brain increased, but the flow to the cerebrum increased proportionately considerably less than did flow to the medulla (e.g., during Step 1, flow

Table 1. Fetal heart rate, blood pressures, blood gases, pH, and oxygen content before and during reduction of uterine blood flow.

	Blood flow reduction				
	Control	Step 1	Step 2	Recovery 1	Recovery 2
Heart rate (beats/min)	167 ± 19	144 ± 45†	140 ± 26‡	188 ± 28	177 ± 19†
Mean aortic pressure (torr)	44.2 ± 3.5	49.6 ± 6.3‡	53 ± 7.5‡	49.7 ± 7.5	46.8 ± 7.6
Umbilical venous pressure (torr)	11.1 ± 4.83	16.6 ± 6.8‡	16.1 ± 6.4‡	12.8 ± 5.2	10.6 ± 4.9
Abdominal inferior vena cava pressure (torr)	3.3 ± 2	4.7 ± 1.9†	4.1 ± 2.7	2.7 ± 1.6	3.8 ± 2.1
Ascending aortic values					
PO_2 (torr)	24.1 ± 2.4	17.0 ± 1.8*	16.3 ± 2.0*	23.5 ± 3.6	22.5 ± 2.3
PCO_2 (torr)	47.3 ± 3.9	53.7 ± 2.9*	59.5 ± 7.4*	49.6 ± 3.4†	50.2 ± 4.0†
pH	7.40 ± 0.013	7.34 ± 0.048‡	7.25 ± 0.084*	7.30 ± 0.08‡	7.32 ± 0.07‡
Base excess	4.60 ± 3.19	2.63 ± 3.33	-2.06 ± 4.98‡	-1.61 ± 5.91	-0.39 ± 4.82
O_2 saturation	67.3 ± 3.9	37.8 ± 7.6*	28.9 ± 8.4*	59.5 ± 9.0†	57.5 ± 9.2‡
Hemoglobin (g/dl)	8.6 ± 1.3	9.5 ± 1.3*	9.7 ± 1.0‡	9.1 ± 1.2†	9.1 ± 1.2†
O_2 content (ml/dl)	7.76 ± 1.1	4.78 ± 0.9*	3.76 ± 1.2*	7.21 ± 1.04	7.04 ± 1.56
Descending aortic values					
PO_2 (torr)	21.7 ± 2.3	15.5 ± 1.8*	14.7 ± 2.5*	21.6 ± 2.3	20.7 ± 2.2
PCO_2 (torr)	50.6 ± 4.5	55.2 ± 3.7†	61.2 ± 7.8*	52.6 ± 4.59	51.0 ± 6.0
pH	7.39 ± 0.026	7.33 ± 0.044*	7.25 ± 0.081*	7.29 ± 0.08‡	7.31 ± 0.07‡
Base excess	5.57 ± 3.57	2.82 ± 3.19	-1.26 ± 4.42†	-1.40 ± 5.33†	-0.70 ± 4.65†
O_2 saturation	58.2 ± 5.8	30.8 ± 5.5*	25.0 ± 7.8*	53.2 ± 9.43	50.0 ± 9.75†
Hemoglobin (g/dl)	8.8 ± 1.3	9.6 ± 1.3*	9.9 ± 1.1*	9.2 ± 1.1‡	9.1 ± 1.3
O_2 content (ml/dl)	6.83 ± 1.2	3.94 ± 0.7*	3.31 ± 1.0*	6.54 ± 1.19	6.14 ± 1.57
Umbilical vein values					
PO_2 (torr)	32.8 ± 3.7	20.8 ± 3.6*	18.2 ± 2.2*	30.9 ± 3.3	31.0 ± 2.7
PCO_2 (torr)	43.9 ± 4.0	50.5 ± 4.9‡	57.9 ± 8.2*	46.6 ± 4.2‡	45.8 ± 3.9
pH	7.42 ± 0.03	7.35 ± 0.05*	7.27 ± 0.08*	7.32 ± 0.08‡	7.34 ± 0.07‡
Base excess	5.24 ± 2.99	2.87 ± 2.93†	-1.67 ± 4.17‡	-1.71 ± 5.14†	-0.60 ± 4.55†
O_2 saturation	86.1 ± 3.1	52.2 ± 14.1*	38.4 ± 11.0*	79.4 ± 7.4‡	78.9 ± 6.6‡
Hemoglobin (g/dl)	8.5 ± 1.3	9.5 ± 1.4*	9.8 ± 1.1*	9.1 ± 1.1‡	8.9 ± 1.2
O_2 content (ml/dl)	9.78 ± 1.5	6.5 ± 1.7*	5.02 ± 1.5*	9.59 ± 1.18	9.41 ± 1.46
Abdominal inferior vena cava values					
PO_2 (torr)	17.1 ± 2.0	11.5 ± 2.0*	10.3 ± 3.0*	16.8 ± 2.5	16.6 ± 2.1
PCO_2 (torr)	54.2 ± 3.3	60.4 ± 2.4‡	69.0 ± 8.4‡	59.4 ± 5.7†	56.9 ± 4.2
pH	7.37 ± 0.03	7.31 ± 0.04*	7.20 ± 0.08*	7.25 ± 0.09‡	7.28 ± 0.07‡
Base excess	5.78 ± 3.15	2.67 ± 3.62†	-1.79 ± 4.27‡	-2.03 ± 5.76†	-0.68 ± 4.69†
O_2 saturation	40.3 ± 6.4	17.0 ± 7.3*	11.4 ± 3.7*	31.9 ± 4.3†	32.8 ± 9.3
Hemoglobin (g/dl)	8.9 ± 1.4	8.7 ± 1.3‡	9.9 ± 1.2‡	9.4 ± 1.1‡	9.2 ± 1.2
O_2 content (ml/dl)	4.85 ± 1.28	2.24 ± 1.16*	1.54 ± 0.56*	4.01 ± 0.57	4.11 ± 1.42
Superior vena cava values					
PO_2 (torr)	18.7 ± 1.9	12.6 ± 1.1*	12.8 ± 2.9*	18.0 ± 2.7	18.4 ± 1.4
PCO_2 (torr)	51.2 ± 4.6	56.9 ± 3.9‡	63.0 ± 13.5	55.8 ± 4.6†	53.4 ± 2.9
pH	7.37 ± 0.03	7.32 ± 0.04*	7.24 ± 0.08‡	7.27 ± 0.09‡	7.30 ± 0.08†
Base excess	5.20 ± 3.08	2.81 ± 4.07	-2.14 ± 2.67†	-1.83 ± 5.87†	-0.71 ± 5.30†
O_2 saturation	45.7 ± 6.4	21.7 ± 5.6*	21.7 ± 10.3‡	38.6 ± 6.5‡	42.0 ± 7.1
Hemoglobin (g/dl)	8.9 ± 1.4	10.0 ± 1.1‡	10.1 ± 1.1	9.3 ± 1.2	9.3 ± 1.2
O_2 content (ml/dl)	5.44 ± 1.11	2.88 ± 0.64*	2.87 ± 1.26‡	4.76 ± 0.73†	5.24 ± 1.12
Superior sagittal sinus values					
PO_2 (torr)	17.4 ± 0.9	13.5 ± 0.9†	14.0 ± 2.0	15.9 ± 1.4	16.1 ± 1.2
PCO_2 (torr)	52.9 ± 5.0	55.1 ± 2.8	62.9 ± 9.5	55.8 ± 2.8	56.0 ± 2.6
pH	7.38 ± 0.03	7.33 ± 0.05	7.26 ± 0.10	7.38 ± 0.09	7.30 ± 0.09
Base excess	5.80 ± 3.61	2.73 ± 5.28	-0.10 ± 5.60	-0.90 ± 7.26	0.40 ± 6.55
O_2 saturation	41.0 ± 1.9	24.5 ± 3.3‡	21.3 ± 9.2†	33.7 ± 4.6	32.9 ± 4.7
Hemoglobin (g/dl)	9.7 ± 1.0	10.4 ± 0.9†	10.3 ± 1.2	10.0 ± 1.1	9.9 ± 1.3
O_2 content (ml/dl)	5.3 ± 0.4	3.4 ± 0.5†	2.9 ± 1.1	4.5 ± 0.2	4.3 ± 0.6

Values are means ± SD, n=9.
* n=4; † P<0.05, ‡ P<0.01, * P<0.001

Table 2A. Fetal combined ventricular output and organ blood flow before and during reduction in uterine blood flow.

	Control	Step 1	Step 2
Combined ventricular output§	478 ± 94	467 ± 126	419 ± 102
Umbilical blood flow (ml/min/kg)	213 ± 55	226 ± 87	209 ± 91
Total body blood flow (ml/min/kg)	315 ± 63	254 ± 74	247 ± 45
		Organ blood flow (ml/min/100g)	
Brain	87.4 ± 20.6	151.3 ± 53.9§	154.3 ± 26.3¶
Heart	163.1 ± 46.5	276.1 ± 79.9¶	367.8 ± 153.5§
Upper carcass	21.6 ± 4.7	15.8 ± 7.4‡	12.5 ± 5.9§
Scalp	33.7 ± 10.4	21.7 ± 8.1‡	14.5 ± 10.2‡
Body skin	23.0 ± 6.3	12.9 ± 7.3‡	9.76 ± 5.9§
Upper body, total* (ml/min/kg)	113 ± 24	112 ± 30	107 ± 27
Adrenals	174.3 ± 118.6	648.4 ± 251.6¶	656.9 ± 373.6§
Kidneys	154.8 ± 40.2	130.9 ± 50.3	107.7 ± 42.6
Spleen	345.1 ± 244.7	305.1 ± 307.4	268.9 ± 224.7
Small gut	89.9 ± 29.8	63.5 ± 33.4	61.5 ± 12.6
Large gut	41.3 ± 10.6	41.4 ± 24.5	39.0 ± 9.8
Lower carcass	19.0 ± 5.0	15.3 ± 9.2	11.8 ± 5.2§
Body skin	26.1 ± 13.7	16.5 ± 9.1	13.0 ± 11.0‡
Lower body, total* (ml/min/kg)	138 ± 35	120 ± 60	100 ± 33‡
Lungs	162.2 ± 74.4	59.6 ± 27.4§	106.4 ± 174.9

Values are means ± SD, n=9.
‡ P<0.05; § P<0.01; ¶ P<0.001.

Table 2B. The % distribution of fetal combined ventricular output before and during reduction in uterine blood flow.

	Control	Step 1	Step 2
Combined ventricular output	100	100	100
Umbilical blood flow (ml/min/kg)	44.0 ± 9.3	46.4 ± 12.7	44.4 ± 10.3
Total body blood flow (ml/min/kg)	56.0 ± 9.3	53.6 ± 12.7	55.6 ± 10.3
Brain	3.00 ± 1.11	6.27 ± 4.30‡	6.66 ± 3.55§
Heart	2.55 ± 0.62	4.54 ± 1.38§	8.85 ± 6.01‡
Upper carcass	15.91 ± 4.48	14.60 ± 5.60‡	12.55 ± 6.4‡
Scalp	0.21 ± 0.07	0.15 ± 0.06‡	0.10 ± 0.06‡
Body skin	0.17 ± 0.09	0.09 ± 0.04‡	0.08 ± 0.04‡
Upper body, total	23.0 ± 5.4	29.0 ± 6.2§	30.9 ± 12.0‡
Adrenals	0.06 ± 0.04	0.21 ± 0.13§	0.22 ± 0.15‡
Kidneys	2.34 ± 0.76	1.95 ± 0.75	1.70 ± 0.57
Spleen	1.01 ± 0.71	0.93 ± 0.92	0.91 ± 0.75‡
Small gut	2.65 ± 1.47	2.02 ± 1.33	2.23 ± 1.19
Large gut	0.27 ± 0.12	0.27 ± 0.16	0.30 ± 0.12
Lower carcass	13.82 ± 2.70	10.26 ± 4.54	9.25 ± 3.8§
Body skin	0.16 ± 0.06	0.11 ± 0.06	0.08 ± 0.03§
Lower body, total†	25.4 ± 4.3	21.5 ± 7.4	19.7 ± 5.7§
Lungs	11.81 ± 5.12	5.08 ± 3.14§	7.57 ± 9.84

Values are means ± SD, n=9.
† not including umbilical blood flow; ‡ P<0.05; § P<0.01; ¶ P<0.001.

to the cerebrum increased by 60%, but that to the medulla increased 140%). Choroid plexus flow tended to decrease during Step 2, but the fall was not significant.

During Step 2 reduction in uterine blood flow, adrenal gland vascular resistance fell from 0.84 ± 1.57 to 0.10 ± 0.06 mmHg/ml/min/100 g, and resistances also fell, in myocardium fom 0.27 ± 0.08 to 0.17 ± 1.11, and in brain from 0.49 ± 0.11 to 0.33 ± 0.33. Vascular resistance in the myocardium, brain, and adrenal gland decreased significantly (Table 3). Resistance to blood flow increased during the Step 2 reduction of uterine

blood flow in all other organs. The most dramatic change in vascular resistance occurred in the skin, where a three- to four-fold increase occurred.

Because umbilical blood flow did not change significantly, oxygen delivery to the fetus was proportional to the decrease of umbilical venous oxygen content; thus, during Step 1 and Step 2 of reduction in uterine blood flow, oxygen delivery to the fetus fell by 32% and 50%, respectively (Table 4). This was accompanied by an increase in fetal oxygen extraction and a 44% decrease in oxygen consumption.

Oxygen delivery to the myocardium was maintained, but oxygen delivery to the adrenal glands increased dramatically to about twice control levels. The changes in oxygen delivery to the brain were of great interest. Total oxygen delivery did not change significantly, but delivery to the midbrain and medulla increased during Step 1 reduction in uterine blood flow and returned to control during Step 2. Oxygen delivery to the cerebrum did not change significantly. Related to the fall in blood flow and arterial oxygen content, oxygen delivery to most other organs fell significantly.

Table 3. Vascular resistance before and during step 1 and step 2 of uterine blood flow reduction.

	Control	Step 1	Step 2
Total fetal body*	0.13 ± 0.02	0.20 ± 0.08‡	0.21 ± 0.05¶
Placenta*	0.16 ± 0.03	0.17 ± 0.08	0.22 ± 0.10
Brain	0.49 ± 0.11	0.33 ± 0.11‖	0.33 ± 0.08¶
Heart	0.27 ± 0.08	0.17 ± 0.06‖	0.17 ± 0.11†
Upper carcass	1.99 ± 0.53	3.75 ± 2.32§	5.10 ± 2.82§
Upper body, total*	0.38 ± 0.11	0.44 ± 0.19	0.50 ± 0.18†
Adrenals	0.84 ± 1.57	0.08 ± 0.05	0.10 ± 0.06
Lower carcass	2.32 ± 0.74	5.26 ± 4.82	5.23 ± 2.88§
Lower body, total*†	0.31 ± 0.08	0.52 ± 0.34	0.55 ± 0.21¶

Values are means ± SD, n=9.
* mm Hg/ml/min/kg, † not including umbilical resistance; ‡ P<0.1, § P<0.05, ¶ P<0.01, ‖ P<0.001

Table 4. Oxygen delivery to the fetus and its organs before and during stepwise reduction in uterine blood flow.

	Control	Step 1	Step 2
Fetal DO_2†	21.34 ± 6.75	14.26 ± 4.42¶	10.76 ± 5.8‖
Fetal VO_2†	6.02 ± 1.35	5.08 ± 2.56	3.47 ± 2.44§
Fetal O_2 extraction (%)	30.2 ± 7.3	38.0 ± 13.5§	33.0 ± 12.8
Upper body DO_2†	8.58 ± 1.42	5.25 ± 1.43‖	3.85 ± 1.18‖
Upper body VO_2†*	2.56 ± 0.71	1.98 ± 0.60	1.54 ± 0.54§
Upper body O_2 extraction (%)*	29.3 ± 7.1	40.1 ± 14.1§	38.4 ± 7.6¶
Lower body DO_2†	9.24 ± 2.27	4.73 ± 2.56¶	3.38 ± 1.73‖
Lower body VO_2†	2.72 ± 0.92	2.31 ± 1.63	1.86 ± 1.07§
Lower body O_2 extraction (%)	29.9 ± 8.4	47.7 ± 13.5‖	52.6 ± 14.7‖
Upper carcass DO_2††	1.66 ± 0.34	0.76 ± 0.39‖	0.48 ± 0.28‖
Upper carcass VO_2††	0.52 ± 0.20	0.41 ± 0.19	0.26 ± 0.15§
Lower carcass DO_2††	1.27 ± 0.33	0.60 ± 0.38	0.41 ± 0.23
Lower carcass VO_2††	0.38 ± 0.14	0.29 ± 0.23	0.23 ± 0.14¶
Brain DO_2††**	6.71 ± 1.45	6.99 ± 1.75	5.73 ± 1.93
Brain VO_2††**	2.46 ± 0.46	2.30 ± 1.09	2.25 ± 0.92
Brain O_2 extraction (%)**	36.4 ± 3.8	29.4 ± 13.0	34.2 ± 10.0
		Organ O_2 delivery††	
Brain	6.71 ± 1.45	6.99 ± 1.75	5.73 ± 1.93
Heart	12.29 ± 2.19	12.79 ± 2.83	12.38 ± 3.05
Adrenals	10.83 ± 6.75	24.78 ± 9.25¶	19.15 ± 8.02¶

Values are means ± SD, n=9.
Paired t-test; * n=7, ** n=4; † ml/min/kg, †† ml/min/100g; ‡ P<0.10, §P<0.05¶,P<0.01,‖ P<0.001.

The most striking decrease in oxygen delivery occurred to the fetal carcass, and particularly to the skin, where it dropped to about 25% of control values.

Oxygen consumption of the brain, as calculated from total cerebral blood flow and oxygen content difference between ascending aortic and sagittal sinus blood, did not change significantly during uterine blood flow reduction.

Distribution of umbilical venous blood flow to liver and ductus venosus

The proportion of umbilical venous blood shunted through the ductus venosus increased slightly during Step 2 of uterine blood flow reduction (from 44.6 ± 18.6% to 53.0 ± 19.8% , $P<0.05$) at the expense of the proportion of umbilical venous blood distributed to the liver (which was reduced from 55.4 ± 18.6% to 47.0 ± 19.8%, $P<0.02$).

Total hepatic blood flow was 386 ± 134 ml/min/100 g liver during the control period; umbilical venous, portal venous, and hepatic arterial blood contributed 78%, 20%, and 2% of the total, respectively. Uterine blood flow reduction did not influence total hepatic blood flow significantly, but there was a tendency for hepatic flow to fall during Step 2. There were no significant changes in the relative proportions obtained from umbilical and portal veins, and the hepatic artery. There were also no significant changes in total flow or relative proportions of flow from various sources to the right or left liver lobes.

During the control period, total liver oxygen delivery was 35.1 ± 16.3 ml/min/100 g liver; it fell 39% and 58% during Step 1 and Step 2 of uterine blood flow reduction, respectively. These decreases in oxygen delivery were largely related to the 39% and 58% fall in oxygen delivery from the umbilical veins and to a lesser extent to the fall in oxygen derived from the portal vein, although the latter fell to a greater degree (by 56% and 66%, respectively) during the two steps of uterine blood flow reduction. The reduction in oxygen delivery was equally distributed between the left and right lobes of the liver.

Distribution of ductus venosus blood flow and oxygen delivery

Although umbilical venous return did not change with reduction in uterine blood flow, the proportion of the cardiac output directed to the ductus venosus increased (Table 5). The distribution of ductus venosus blood and the amount of oxygen delivered to fetal organs from ductus blood are shown in Table 6. The proportion of ductus venosus blood distributed to the brain and heart increased, but that to the upper carcass decreased, so that the percentage of ductus venosus blood shunted through the foramen ovale and distributed to the upper body did not change significantly. Ductus venosus-derived oxygen delivery to the brain was maintained, and that to the heart increased 54% during Step 2 even though total ductus venosus-derived oxygen delivery to the upper body segment fell 34% to 1.59 ± 0.7 ml/min/100 g.

The proportions of ductus venosus blood flow distributed and the resulting blood flows to the lower body organs and to the placenta were maintained during uterine blood flow reduction. Because umbilical venous oxygen content fell, the oxygen delivery from the ductus venosus blood fell 50% to the lower body and 32% to the placenta. Ductus venosus-derived oxygen delivery to the adrenal glands increased. Ductus venosus-derived blood flow and oxygen delivery to the lungs fell significantly.

Abdominal inferior vena caval blood flow distribution and oxygen delivery

Abdominal inferior vena caval blood flow and its proportion of combined ventricular output decreased after Step 2 of uterine blood flow reduction (Table 5). The distribution of abdominal inferior vena caval blood to fetal organs is shown in Table 7. The proportion of this blood delivered to the upper body increased, but actual

Table 5. The effects of stepwise reduction of uterine blood flow on umbilical venous flow through the ductus venosus and to the liver, and on abdominal inferior vena caval and superior vena caval flows.

	Control	Step 1	Step 2
Ductus venosus flow			
QDV (ml/min/kg)	94.4 ± 37.0	113.0 ± 64.5	113.5 ± 55.9
QDV (% combined ventricular output)	17.7 ± 6.2	22.4 ± 10.9	23.8 ± 9.4‡
Liver blood flow			
Q Liver (ml/min/kg)*	123.5 ± 58.1	118.5 ± 38.6	98.7 ± 56.3
Q Liver (% combined ventricular output)*	23.1 ± 9.3	24.6 ± 6.2	20.9 ± 8.7
Abdominal inferior vena cava flow			
QIVCa (ml/min/kg)	137.8 ± 35.2	119.7 ± 60.1	100.4 ± 33.1†
QIVCa (% combined ventricular output)	25.4 ± 4.3	21.5 ± 7.4	19.7 ± 5.7‡
Superior vena cava flow			
QSVC (ml/min/kg)	112.6 ± 24.2	112.2 ± 29.9	106.8 ± 26.7
QSVC (% combined ventricular output)	23.0 ± 5.4	29.0 ± 6.2‡	30.9 ± 12.0†

Values are means ± SD, n=9.
* Umbilical venous; † $P<0.05$, ‡ $P<0.01$

blood flow did not change, resulting in a 70% fall in oxygen delivery to the upper body segment from the abdominal inferior vena cava. The fraction of abdominal inferior vena caval blood distributed to the lower body decreased, and that to the placenta did not change. This was associated with the decrease in blood flow to most of the lower body organs, except that to the adrenals and the placenta. Thus, oxygen delivered from the abdominal inferior vena cava to the lower body segment and that to the placenta fell by 81% and 76%, respectively, whereas that to the adrenals was maintained. Table 7 shows the blood flow and oxygen delivered from abdominal inferior vena cava to individual organs.

Superior vena caval blood flow, distribution, and oxygen delivery

Superior vena caval blood flow did not change significantly, but its contribution to the combined ventricular output increased during reduction of uterine blood flow (Table 5). The proportion of superior vena caval blood distributed to the fetal body decreased (Table 8). Although a greater portion of the superior vena caval blood was shunted through the foramen ovale to the upper body, the actual amounts of blood and oxygen delivered to the upper body from the superior vena cava were small (Table 8). Reduction of uterine blood flow decreased the proportion of superior vena caval

Table 6. Distribution of ductus venosus blood, as a percentage of total, to fetal organs before and during stepwise reduction of uterine blood flow.

	%QDV		
	Control	Step 1	Step 2
Total body	59.4 ± 9.1	56.7 ± 12.5	58.3 ± 9.0
Brain	4.1 ± 1.3	8.1 ± 4.0†	8.6 ± 4.4†
Heart	3.0 ± 0.8	6.5 ± 1.9‡	9.8 ± 7.4
Upper carcass	19.2 ± 5.1	16.0 ± 5.4†	13.0 ± 6.1‡
Upper body, total	27.8 ± 7.0	32.2 ± 5.9	32.8 ± 10.6
Adrenals	0.1 ± 0.03	0.2 ± 0.1‡	0.2 ± 0.2†
Lower carcass	15.6 ± 4.5	15.6 ± 4.5	11.8 ± 7.2
Lower body, total	25.1 ± 4.4	21.8 ± 8.2	21.1 ± 7.7
Placenta	40.6 ± 9.1	43.4 ± 12.5	41.7 ± 9.0
Lungs	6.24 ± 2.81	2.20 ± 1.17‡	3.96 ± 4.7
Ductus venosus derived blood flow to fetal organs			
		DV-Derived blood flow (ml/min/100g)	
Total body*	56.1 ± 24.4	60.4 ± 30.7	63.4 ± 28.1
Brain	20.6 ± 6.8	46.3 ± 26.5†	48.1 ± 23.6‡
Heart	37.7 ± 22.2	91.1 ± 49.5‡	125.6 ± 81.6‡
Upper carcass	5.1 ± 2.4	4.8 ± 3.1	4.1 ± 3.1
Upper body, total*	26.1 ± 11.9	34.6 ± 17.4	35.2 ± 19.1†
Adrenals	38.7 ± 22.9	141.0 ± 78.4‡	173.3 ± 133.0†
Lower carcass	4.0 ± 1.7	3.7 ± 2.8	3.5 ± 2.6
Lower body, total*	23.8 ± 10.7	23.0 ± 14.1	22.2 ± 11.1
Placenta*	37.1 ± 17.0	51.0 ± 42.5	48.8 ± 33.0
Lungs	37.8 ± 31.8	15.1 ± 11.8†	27.9 ± 41.9
Ductus venosus-derived oxygen delivery to fetal organs			
		DV-Derived DO_2 (ml/min/100g)	
Total body*	5.20 ± 1.58	3.73 ± 1.77†	3.03 ± 1.38‡
Brain	1.95 ± 0.47	2.75 ± 1.20	2.19 ± 0.73
Heart	3.52 ± 1.70	5.62 ± 3.14†	5.43 ± 3.08†
Upper carcass	0.47 ± 0.17	0.30 ± 0.19‡	0.20 ± 0.13§
Upper body, total*	2.41 ± 0.80	2.10 ± 0.91	1.59 ± 0.70§
Adrenals	3.54 ± 1.68	8.59 ± 4.59‡	7.81 ± 4.94†
Lower carcass	0.38 ± 0.13	0.24 ± 0.20§	0.18 ± 0.14§
Lower body, total*	2.20 ± 0.71	1.45 ± 0.90	1.11 ± 0.62‡
Placenta*	3.55 ± 1.72	2.99 ± 2.28	2.41 ± 1.93‡
Lungs	1.42 ± 0.88	0.46 ± 0.31‡	0.73 ± 1.31

Values are means ± SD, n=9.
* ml/min/kg; † P<0.05, ‡ P<0.01, § P<0.001.

Table 7. Distribution of QIVCa to fetal organs before and during stepwise reduction of uterine blood flow.

	%QIVCa		
	Control	Step 1	Step 2
Total body	56.0 ± 9.3	53.6 ± 12.7	55.6 ± 10.3
Brain	3.3 ± 1.2	7.4 ± 4.2‡	8.4 ± 4.9‡
Heart	2.6 ± 0.6	5.5 ± 1.4‡†	8.9 ± 6.0†
Upper carcass	15.9 ± 4.5	14.6 ± 5.6	12.5 ± 6.4†
Upper body, total	23.0 ± 5.4	29.0 ± 6.2‡	30.9 ± 12.0
Adrenals	0.1 ± 0.04	0.2 ± 0.1‡	0.2 ± 0.2‡
Lower carcass	13.8 ± 2.7	10.3 ± 4.5†	9.2 ± 3.8‡
Lower body, total	25.4 ± 4.3	21.5 ± 7.4	19.7 ± 5.7‡
Placenta	44.0 ± 9.3	46.4 ± 12.7	44.4 ± 10.3
Lungs	7.32 ± 2.96	2.67 ± 1.26	4.55 ± 6.16
QIVCa-derived blood flow to fetal organs			
		QIVCa-Derived blood flow (ml/min/100g)	
Total body*	145.0 ± 38.0	130.0 ± 56.8	107.3 ± 30.4
Brain	47.7 ± 18.5	89.7 ± 30.8‡†	83.0 ± 25.3‡†
Heart	87.1 ± 31.9	168.2 ± 58.5‡	199.3 ± 86.8‡
Upper carcass	11.7 ± 4.3	10.7 ± 6.3	7.2 ± 4.4†
Upper body, total*	59.6 ± 19.8	69.3 ± 27.8	57.7 ± 21.3
Adrenals	86.3 ± 56.5	307.1 ± 131.2‡†	263.9 ± 131.3‡†
Lower carcass	9.8 ± 2.6	7.5 ± 4.5	5.3 ± 3.0‡
Lower body, total*	65.4 ± 16.1	53.9 ± 28.3	39.2 ± 17.2†
Placenta*	113.8 ± 41.3	106.4 ± 39.6	90.9 ± 49.3
Lungs	106.3 ± 52.6	37.8 ± 23.3‡	80.8 ± 156.2
QIVCa-derived DO_2 to fetal organs			
		QIVCa-Derived blood flow (ml/min/100g)	
Total body*	7.10 ± 2.83	2.68 ± 1.46‡	1.68 ± 0.81‡†
Brain	2.37 ± 1.24	1.90 ± 1.14	1.30 ± 0.70†
Heart	4.16 ± 1.81	3.44 ± 1.69	2.90 ± 1.63
Upper carcass	0.58 ± 0.29	0.22 ± 0.13‡	0.11 ± 0.09‡†
Upper body, total*	2.91 ± 1.32	1.42 ± 0.75†	0.87 ± 0.51‡†
Adrenals	3.82 ± 2.52	6.74 ± 5.40	3.78 ± 1.76
Lower carcass	0.48 ± 0.19	0.15 ± 0.10‡†	0.09 ± 0.06‡†
Lower body, total*	3.19 ± 1.21	1.12 ± 0.72‡	0.62 ± 0.36‡†
Placenta*	5.89 ± 3.57	2.23 ± 1.04†	1.46 ± 0.96‡
Lungs	4.06 ± 2.69	0.54 ± 0.23‡	0.78 ± 1.32‡
QIVCa-derived fractional DO_2 to fetal organs			
		QIVCa-Derived DO_2 (%)	
Total body	47.5 ± 12.8	35.7 ± 12.9	30.5 ± 11.3‡†
Brain	51.9 ± 16.7	40.3 ± 17.5†	35.9 ± 15.9‡
Heart	53.7 ± 16.2	39.6 ± 17.8†	35.2 ± 16.6‡
Upper carcass	52.5 ± 17.0	39.1 ± 16.7†	34.8 ± 17.3‡†
Upper body, total	52.7 ± 16.8	39.6 ± 16.9	34.7 ± 15.8
Adrenals	36.0 ± 15.8	32.6 ± 10.9	26.0 ± 9.20
Lower carcass	43.4 ± 11.2	30.5 ± 10.2	25.7 ± 10.0‡†
Lower body, total	45.6 ± 11.3	33.0 ± 10.4	26.7 ± 8.80‡†
Placenta	41.4 ± 18.9	29.1 ± 14.1	24.9 ± 12.5‡†
Lungs	55.5 ± 14.0	43.2 ± 10.4‡	34.4 ± 9.1‡

Values are means ± SD, n=9.
* ml/min/kg; † $P<0.05$, ‡ $P<0.01$.

blood flow to the lungs, resulting in a significant fall in actual flow and oxygen delivered to this organ.

Partitioning of venous returns in blood flow and oxygen delivery to fetal organs

To examine the partitioning of each of the venous returns in the total arterial blood flow and oxygen delivery to the fetal organs and the effect of graded reduction in uterine blood flow thereon, we first calculated the total blood flow and oxygen delivery to the upper and lower segments of the fetal body. The changes described below are those observed during Step 2 of reduction in uterine blood flow. There were no changes in blood flow to either the upper body or the placenta, but there was a significant decrease (27%) in that to the lower body segment. This was accompanied by a 55%, 63%, and 52% fall in oxygen delivery to upper body, lower body, and placenta, respectively.

The proportions of total blood flow and oxygen delivery to the upper and lower segments of the fetal body and to the lungs contributed by ductus venosus, inferior abdominal vena cava, and superior vena cava (which may not constitute 100% because blood is also derived from hepatic veins, pulmonary veins, and coronary sinus) are changed during reduction in uterine blood flow. Ductus venosus blood flow constituted 23% of the total blood flow to the upper body organs, and

Table 8. Distribution of QSVC to fetal organs before and during stepwise reduction of uterine blood flow.

	%QSVC		
	Control	Step 1	Step 2
Total body	46.2 ± 8.2	36.8 ± 11.5†	37.5 ± 8.6
Brain	0.1 ± 0.1	0.4 ± 0.4†	0.8 ± 0.9
Heart	0.1 ± 0.1	0.3 ± 0.3	1.1 ± 1.6
Upper carcass	1.1 ± 0.4	2.1 ± 1.0†	1.9 ± 0.8†
Upper body, total	1.3 ± 0.5	2.9 ± 1.4‡	4.0 ± 3.1
Adrenals	0.1 ± 0.03	0.3 ± 0.2‡	0.4 ± 0.3†
Lower carcass	17.5 ± 3.5	14.0 ± 6.6	11.8 ± 5.4‡
Lower body, total	31.1 ± 6.1	28.3 ± 10.5	25.4 ± 8.9
Placenta	53.8 ± 8.2	63.2 ± 11.5†	62.5 ± 8.6
Lungs	13.5 ± 6.2	5.4 ± 2.4‡	7.8 ± 7.6
QSVC-derived blood flow to fetal organs			
		QSVC-Derived blood flow (ml/min/100g)	
Total body*	52.4 ± 15.8	42.1 ± 17.2	39.1 ± 10.4†
Brain	0.27 ± 0.27	2.24 ± 2.33	4.83 ± 4.61†
Heart	1.22 ± 1.08	4.31 ± 4.44	15.03 ± 19.93
Upper carcass	0.36 ± 0.14	0.68 ± 0.39†	0.61 ± 0.28†
Upper body, total*	1.45 ± 0.60	3.27 ± 1.75‡	4.47 ± 3.25†
Adrenals	58.4 ± 27.0	220.9 ± 105.5‡	271.9 ± 188.1‡
Lower carcass	5.5 ± 1.7	4.6 ± 2.6	3.6 ± 1.8†
Lower body, total*	35.4 ± 11.4	32.7 ± 15.2	27.5 ± 10.5
Placenta*	58.7 ± 13.4	67.7 ± 16.5	65.5 ± 20.4
Lungs	55.9 ± 25.5	21.3 ± 7.7‡	25.6 ± 21.5†
QSVC-derived DO_2 to fetal organs			
		QSVC-Derived DO_2 (ml/min/100g)	
Total body*	2.68 ± 0.6	1.16 ± 0.57‡†	1.10 ± 0.44‡
Brain	0.02 ± 0.02	0.08 ± 0.09	0.10 ± 0.10
Heart	0.06 ± 0.06	0.15 ± 0.17	0.28 ± 0.34
Upper carcass	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01
Upper body, total*	0.08 ± 0.04	0.10 ± 0.07	0.09 ± 0.06
Adrenals	2.72 ± 0.99	5.84 ± 3.25	4.91 ± 2.34
Lower carcass	0.28 ± 0.09	0.13 ± 0.08‡†	0.11 ± 0.06‡†
Lower body, total*	1.72 ± 0.38	0.90 ± 0.47‡†	0.78 ± 0.41‡
Placenta*	3.08 ± 1.05	1.82 ± 0.68‡	1.64 ± 0.70†
Lungs	2.04 ± 0.87	0.41 ± 0.19‡	0.61 ± 0.41‡

Values are means ± SD, n=9.
* ml/min/kg; † $P<0.05$, ‡ $P<0.01$.

this proportion increased to 33% during reduction in uterine blood flow. Abdominal inferior vena caval blood constituted a larger fraction (53%) of total blood flow to the upper body, and this was maintained during reduction of uterine blood flow. The contribution of superior vena caval blood to the total upper body blood flow also increased from about 1% to 4%, but it still constituted a small fraction of the total.

The ductus venosus blood contributed 28% of the total amount of oxygen delivered to the upper body organs, and this proportion increased to 41%, whereas that contributed by the abdominal inferior vena caval blood decreased from 34% to 23% during reduction in uterine blood flow.

Ductus venosus blood contributed 17% of the total blood flow and 24% of the total oxygen delivery to the lower body segment, and even though this fraction of blood flow increased by only 5% during uterine blood flow reduction, the proportion of oxygen delivered from ductus venosus blood increased by 9%. The fraction of abdominal inferior vena caval blood flow to the total lower body organs decreased from 47% to 39%, and there was a dramatic fall in oxygen delivery from 35% to 18%. Blood returning from the superior vena cava provided 26% of the blood and 19% of the oxygen delivered to the lower body segment, and these proportions did not change significantly during reduction in uterine blood flow. Inferior vena caval blood constituted the major fraction of total pulmonary blood flow and oxygen delivery, but in spite of an increase in the proportion of inferior vena caval blood flow to the lungs during uterine blood flow reduction, oxygen delivery decreased from this source, whereas that from the ductus venosus increased and that from the superior vena cava was maintained.

Discussion

The effects on the fetal circulation of reducing oxygen supply by decreasing umbilical blood flow by cord compression (Itskovitz *et al.*, 1987), and by administering a low-oxygen gas mixture to the mother (Cohn *et al.*, 1974) have been reported previously from our laboratory. In this study, we examined the changes resulting from decreasing fetal oxygen supply by acute reduction of uterine blood flow. To compare this type of stress with the other forms of acute fetal insult, we attempted to effect similar degrees of reduction of oxygen delivery to the fetus of about 30% and 50%, as we had produced by umbilical cord compression. In preliminary studies, we had shown that umbilical-placental blood flow does not change significantly during uterine blood flow reduction. It was therefore possible to estimate the degree of decrease in oxygen delivery by estimating the oxygen content of umbilical venous blood. In this discussion, we have compared and contrasted the effects of a 50% reduction of oxygen delivery induced by the three different types of stress.

Fetal blood gas changes with reduced uterine blood flow were similar to those occurring with maternal hypoxemia, but different from those associated with decreased umbilical blood flow. The fall in carotid arterial PO_2 and pH was most pronounced with maternal hypoxemia, then with reduced uterine blood flow, and least severe with umbilical cord compression. Another important difference was the significant increase in carotid arterial PCO_2 associated with reduced uterine blood flow. This difference in arterial PCO_2 could be related to CO_2 production, but is much more likely related to differences in placental perfusion. During uterine blood flow reduction, umbilical blood flow does not change; there is thus a considerable decrease in uterine:umbilical perfusion relationships, which could account for the increase in fetal PCO_2. With reduced umbilical blood flow, there is an increase in uterine:umbilical perfusion relationship, and this could more effectively remove fetal CO_2. Furthermore, umbilical cord compression increases umbilical venous pressure markedly, and this could distend umbilical vessels at the placental exchange site and increase the vascular surface area and diffusing capacity. These changes could well account for the lack of significant increase in fetal blood PCO_2 with umbilical cord compression.

In preliminary studies, we showed that constriction of the common uterine hypogastric artery causes a considerable decrease in distal uterine arterial pressure as well as reducing uterine blood flow. Our observation that umbilical blood flow did not change during the decrease in uterine blood flow confirms our previous observation that there is no significant interaction between uterine and umbilical blood flows in the sheep placenta (Berman, Goodlin, Heymann & Rudolph 1975).

Hepatic and ductus venosus blood flow and oxygen delivery

The responses of umbilical blood flow and its distribution to reduced uterine blood flow were similar to those observed with fetal hypoxemia (Bristow *et al.*,1983). While umbilical venous return did not change, there was a trend for ductus venosus flow to increase and for hepatic flow to decrease, but the changes were not statistically significant. However, the proportion of umbilical venous blood traversing the ductus venosus increased by about 10%. The mechanisms responsible for this redistribution of umbilical venous blood have not been resolved. Edelstone *et al.* (1980) suggested that the ductus venosus responds passively to transluminal pressure changes. Umbilical venous pressure increased significantly from 11.1 to 16.1 mmHg during 50% reduction in oxygen delivery to the fetus in our study. However, the pressure gradient between the umbilical veins and the inferior vena cava increased significantly from about 8 to 12 mmHg in association with increased ductus venosus blood flow. These changes would suggest that there is no significant relaxant effect of the reduced umbilical venous oxygen content on the ductus venosus to cause the increase in

ductus venosus blood flow. We suggest that vasoconstriction in the hepatic circulation is the primary mechanism resulting in the redistribution of umbilical blood flow. The site of constriction in the hepatic circulation requires study, but the mechanism could be related to neural or hormonal influences resulting from arterial hypoxemia.

Umbilical blood flow reduction is also associated with preferential redistribution of umbilical venous blood through the ductus venosus, but hepatic blood flow is markedly reduced. Similarly, oxygen delivery to the liver is reduced considerably with uterine blood flow reduction because umbilical venous oxygen content is reduced. However, the reduction of oxygen delivery with umbilical blood flow reduction is much more marked, probably as a result of decreased umbilical venous perfusing pressure.

General circulatory responses

Reduction in uterine blood flow is associated with fetal bradycardia of mild degree and an increase in fetal aortic pressure. These changes are similar to those occurring with maternal hypoxemia and with umbilical cord compression, but of different degree. Also, whereas combined ventricular output decreased with maternal hypoxemia and with cord compression, it did not change significantly with uterine blood flow reduction. The general circulatory changes observed during uterine blood flow reduction were similar to those reported by Yaffe *et al.* (1987). However, they noted no significant changes in blood flow or resistance in the peripheral circulation (carcass), except with extreme reduction in uterine blood flow. In our study, blood flow to the carcass fell and vascular resistance increased significantly. It is difficult to explain these differences, but they could be related to variation in the degree of hypoxemia produced. In our study, descending aortic PO_2 dropped to 15.5 and 14.7 torr, whereas in the study of Yaffe *et al.*, it fell to 18.0, 12.7, and 11.0 with varying degrees of uterine blood flow reduction. The unusual response of a drop in cerebral blood flow and increase in cerebral vascular resistance that they observed with severe reduction of uterine blood flow was almost certainly related to circulatory collapse with a fall in combined ventricular output.

There were several important differences in the effects of the three methods of inducing reduced fetal oxygen delivery, on the distribution of cardiac output and on blood flow to individual organs. Thus, myocardial blood flow increased markedly during maternal hypoxemia, considerably less so during uterine blood flow reduction, and not at all during umbilical blood flow reduction. Similarly, blood flow to the brain and adrenal glands increased most with maternal hypoxemia, less so with uterine blood flow reduction, and least during umbilical cord compression. Blood flow to these three organs is greatly influenced by the oxygen content of perfusing blood. Differences in the magnitude of fall in arterial blood PO_2 and oxygen saturation could, at least in part, explain these blood flow changes. Thus, during maternal hypoxemia fetal arterial PO_2 was reduced to about 12 torr, whereas in the current study PO_2 fell to 16.3 torr, and with cord compression it fell to only 17.7 torr.

Umbilical-placental blood flow was maintained both during maternal hypoxemia and uterine blood flow reduction; however, fetal body blood flow fell markedly with hypoxemia, but did not change significantly with uterine blood flow reduction. Fetal body blood flow was also maintained during umbilical cord compression. The most important change contributing to the decrease in body flow is the reduction in blood flow to the peripheral circulation, including skin, muscle, and bone. Peripheral vasoconstriction results from sympathetico-adrenal stimulation by chemoreflex mechanisms. Peripheral vasoconstriction and reduced blood flow are abolished in fetal lambs by denervation of the aortic and carotid sinuses (Itskovitz, J. & Rudolph, A. M., unpublished observations) as well as by chemical sympathectomy with 6 hydroxydopamine. Fetal peripheral circulatory responses are marked during maternal hypoxemia and somewhat less prominent during uterine blood flow reduction, and peripheral blood flow is not significantly altered with umbilical cord compression.

These differences can probably also be explained largely on the degree of chemoreflex stimulation in the three types of fetal stress. As mentioned above, with maternal hypoxemia, fetal arterial PO_2 fell markedly to about 12 torr, whereas with uterine blood flow reduction, carotid arterial PO_2 fell less, to 16.3 torr. Umbilical cord compression was associated with even less of a fall of carotid PO_2, to a level of 17.7 torr. The carotid arterial PO_2 fell 5.4 torr with cord compression, but the 7.8 torr fall with uterine flow reduction could account for a difference in hypoxic stimulation of peripheral chemoreceptors. However, an additional factor to be considered is the difference in pH and PCO_2 response, because hypercarbia and acidemia may potentiate the chemoreceptor response to hypoxemia. During umbilical cord compression, arterial pH and PCO_2 did not change significantly, but with reduced uterine blood flow, PCO_2 increased considerably and pH fell.

The relatively greater fall in carotid arterial PO_2 with maternal hypoxemia and reduced uterine flow is related to the fall in umbilical venous PO_2. With umbilical cord compression, umbilical venous PO_2 and oxygen saturation do not fall, and may even rise slightly. Although umbilical blood flow was reduced by 50%, preferential streaming through the ductus venosus, and then through the foramen ovale, contributed an amount of well-oxygenated umbilical venous blood to the left ventricle adequate to prevent a major fall in carotid arterial PO_2.

The magnitude of the fall in carotid arterial PO_2 probably also accounts for the different fetal cardiovascular responses to complete occlusion of the uterine

arteries for two minutes, as studied by Jensen and Lang (1987), as compared with the current study of more prolonged partial occlusion. With complete occlusion, blood flow to the fetal kidney, gut, spleen, and peripheral circulation all fell dramatically; skin flow fell by 90%, whereas with partial occlusion, peripheral circulatory and skin flow decreased modestly, but flow to the other abdominal organs did not change significantly. The decrease in arterial pH was similar in the two studies, to 7.25, but the fall in arterial oxygen content was considerably greater with complete occlusion of the uterine arteries.

Oxygen delivery and oxygen consumption

When fetal oxygen delivery was reduced by umbilical cord compression, it was noted that fetal oxygen consumption was maintained as a result of increased oxygen extraction by the fetal body. It was necessary to produce about a 50% decrease in fetal oxygen delivery to reduce oxygen consumption (Itskovitz *et al.*, 1983). At 50% reduction in oxygen delivery, fetal oxygen extraction increased markedly from a control of 33% to 53%, and there was a 28% fall in fetal oxygen consumption. In the present study, in which we reduced uterine blood flow to produce a 50% decrease in oxygen delivery, total fetal oxygen consumption fell by 44%, and there was only a minimal change in oxygen extraction from 30% to 33%. This difference is probably related to the lower oxygen content of arterial blood perfusing both the upper and lower body when oxygen delivery is reduced to a similar degree by uterine arterial constriction as compared with cord compression. Thus, with umbilical cord compression, ascending aortic oxygen content fell to 5.29 ml/dl, and descending aortic oxygen content to 4.22 ml/dl; with uterine arterial constriction, the levels reached were 3.76 and 3.31 ml/dl, respectively.

Even though total body oxygen consumption fell during uterine blood flow reduction, cerebral oxygen consumption was maintained. This was not related to an increase in oxygen extraction, but rather, to maintenance of oxygen delivery by increasing blood flow. We did not measure oxygen consumption in other body organs, but were able to calculate oxygen consumption in the lower body, which represents the peripheral circulation of the lower trunk and hindlimbs, and also to the upper body. As we have shown previously with maternal hypoxemia (Iwamoto & Rudolph 1985), there was a linear relationship between oxygen delivery and oxygen consumption.

Differential venous flow patterns and oxygen delivery

During uterine blood flow reduction, the proportion of total venous return contributed by the abdominal inferior vena cava decreased, while that derived from the ductus venosus, superior vena cava, and coronary sinus increased. Reduction of umbilical venous return is associated with a marked increase in the proportion of umbilical venous blood that traverses the ductus venosus, whereas with reduced uterine flow, this proportion increases only slightly. However, the volume of ductus venosus-derived blood distributed to upper body organs increases, whereas that contributed from the abdominal inferior vena cava decreases. The oxygen content in umbilical venous blood falls by about 50%, from 9.78 to 5.02 ml/dl (Table 1), whereas that in abdominal inferior vena caval blood falls by 68%, from 4.85 to 1.54 ml/dl. Thus, normally a considerable amount of oxygen delivered to the fetal body is derived from vena caval blood, but during uterine blood flow reduction, blood derived from the ductus venosus becomes increasingly important in oxygen delivery. As can be calculated from the data in Tables 6 and 7, of the total oxygen delivered to the myocardium from the abdominal inferior vena cava and ductus venosus, about 55% is derived from the inferior vena caval blood during the control state, but this falls to 35% during uterine arterial constriction.

Whether distribution of hepatic venous blood is altered during uterine blood flow reduction is not known. Examining possible changes will be important, because hepatic venous blood constitutes almost a quarter of total venous return to the heart.

These studies, in conjunction with those reported previously from our laboratory, demonstrate that fetal cardiovascular responses to various types of stress are clearly different. It will be important to determine the potential effects of differences in effects on blood gases and whether metabolic and hormonal responses also may vary.

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