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Fetal circulatory responses to oxygen lack

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Abstract
The knowledge on fetal and neonatal circulatory physiology accumulated by basic scientists and clinicians over the years has contributed considerably to the recent decline of perinatal morbidity and mortality. This review will summarize the peculiarities of the fetal circulation, the distribution of organ blood flow during normoxemia, and that during oxygen lack caused by various experimental perturbations. Furthermore, the relation between oxygen delivery and tissue metabolism during oxygen lack as well as evidence to support a new concept will be presented along with the principal cardiovascular mechanisms involved. Finally, blood flow and oxygen delivery to the principal fetal organs will be examined and discussed in relation to organ function. The fetal circulatory response to hypoxemia and asphyxia is a centralization of blood flow in favour of the brain, heart, and adrenals and at the expense of almost all peripheral organs, particularly of the lungs, carcass, skin and scalp. This response is qualitatively similar but quantitatively different under various experimental conditions. However, at the nadir of severe acute asphyxia the circulatory centralization cannot be maintained. Then there is circulatory decentralization, and the fetus will experience severe brain damage if not expire unless immediate resuscitation occurs. Future work in this field will have to concentrate on the important questions, what factors determine this collapse of circulatory compensating mechanisms in the fetus, how does it relate to neuronal damage, and how can the fetal brain be pharmacologically protected against the adverse effects of asphyxia.

Introduction

Since Paul Zweifel (1876), an obstetrician, demonstrated for the first time by spectroscopy the transfer of oxygen from the mother to the fetus via the placenta, and since the inspiring early work of Sir Joseph Barcroft (1946), the fetal circulation and its regulation has attracted the interest of many investigators, basic scientists, and clinicians. This is reflected by the increasing number of publications in the field. The resulting accumulation of knowledge on fetal and neonatal circulatory physiology, which has been summarized in a number of excellent reviews (Dawes, 1962, 1968; Rudolph 1981, 1984, 1985; Mott & Walker, 1984), has contributed considerably to the decline of perinatal morbidity and mortality in recent years.

In his monograph, Dawes (1968) reviewed the pioneering earlier work in the field, which was largely based on observations in acutely instrumented fetuses of various species. Many conclusions on the fetal circulation drawn from acute studies under general anaesthesia are still valid, e.g., the general principle of circulatory centralization during asphyxia (Campbell, Dawes, Fishman, Hyman, 1967) and the vascular reflex mechanisms involved (Dawes *et al.*, 1968). However, others, e.g. some of those on the umbilical circulation, had to be reconsidered (Dawes, 1962).

A major step forward towards studying the undisturbed fetus *in utero* was the chronic implantation of catheters and probes into the fetus in the late 1960s (Meschia, Cotter, Breathnack, Barron, 1965). Since then, many experiments were repeated in the absence of anaesthesia. Rudolph extensively reviewed the literature on the circulation and its control of chronically prepared fetal sheep (Rudolph 1973; 1981; 1984; 1985). In many of these studies the microsphere method was used (Rudolph and Heymann, 1967) to measure the distribution of blood flow, and elegant surgical techniques are presented to study various aspects of fetal cardiovascular physiology in this model, particularly that of the placenta, lung, liver, heart, and kidney. In terms of circulatory control of specific organs the lung is one of those studied most intensively. The body of work on the pulmonary circulation has been reviewed recently by Heymann (1984; 1988).

In this review we will present the current knowledge on the distribution of fetal organ blood flow and on changes in it during various experimental perturbations. Most of the work reviewed derives from studies in chronically prepared fetal sheep, because this model has been used by most investigators.

The first part of this review will describe the peculiarities of the fetal circulation and the distribution of combined ventricular output during normoxemia. Then the cardiovascular responses to hypoxemia and asphyxia with respect to the different methods by which a lack of oxygen can be induced will be examined. These include maternal hypoxemia, graded reduction in umbilical blood flow, graded reduction in uterine blood flow, repeated brief arrest of uterine

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blood flow, prolonged arrest of uterine blood flow, reduction in fetal blood volume, and chronic hypoxemia induced by various methods. Furthermore, circulatory responses of immature fetuses to hypoxemia and asphyxia will be described. The following part will focus on the relation between oxygen delivery and tissue metabolism, and evidence to support a new concept will be presented. In the next part the principal cardiovascular mechanisms involved in fetal circulatory responses to oxygen lack will be summarized. In the final part of this review blood flow and oxygen delivery to the principal fetal organs during hypoxemia and asphyxia will be examined and discussed in relation to organ function.

Fetal circulation

There are a number of differences between fetal and adult circulation, most of them being related to the fact that during intrauterine life, the placenta serves as the site of gas exchange rather than the lungs. Hence, the most important features of the fetal circulation are the relatively large proportion of combined output of both cardiac ventricles distributed to the umbilical cord and placenta (45%) and the small proportion distributed to the lungs (10%). This requires special vascular channels, i.e., the foramen ovale and the ductus arteriosus (Botalli), which are unique to the fetus and serve to shunt blood returning to the heart away from the pulmonary circulation (Dawes, 1968; Rudolph, 1985).

This anatomical arrangement permits normally almost equal development of the two sides of the heart, which work in parallel during fetal life, but serially after birth. Furthermore, it allows for preferential streaming of highly oxygenated umbilical venous blood via the ductus venosus (Arantii), thoracic inferior cava, right atrium, foramen ovale, left atrium, left ventricle, and ascending aorta to the upper body segment in general, and to the heart and brain in particular (Barclay, Franklin & Prichard, 1944; Rudolph, 1985).

On the other hand, poorly oxygenated blood returning to the heart from both abdominal inferior and superior vena cava passes through right atrium, right ventricle, pulmonary artery (65%), ductus arteriosus (57%) and descending aorta to the lower body segment (27%) and to the umbilical cord (45%) (Cohn, Sacks, Heymann & Rudolph, 1974; Reuss & Rudolph, 1980).

After gas exchange in the placenta, oxygenated blood returns to the fetal body through the umbilical veins. The common umbilical vein enters the liver, where it joins the portal vein. From the portal sinus several branches supply the right and left liver lobes, and the ductus venosus connects the umbilical vein to the inferior vena cava, thus permitting about 55% of the umbilical venous blood to bypass the liver (Edelstone, Rudolph & Heymann, 1978; Rudolph, 1985). The amount of oxygen delivered to the right and left lobe of the liver is different, because the right lobe receives almost all of the portal venous blood along with umbilical venous blood whereas the left liver lobe is almost exclusively supplied by the umbilical vein (Edelstone *et al.*, 1978). The contribution of hepatic arterial blood to the oxygen supply of the two liver lobes is small (3%).

Although it had been assumed that there is a reasonable admixture of poorly oxygenated abdominal inferior vena caval blood with highly oxygenated umbilical venous blood in the thoracic inferior vena cava, elegant cineangiographic studies of Barclay, Franklin and Prichard (1944) suggested that blood from these sources streams selectively, so that ductus venosus blood preferentially passes through the foramen ovale to the upper body organs. This was confirmed by Behrman and colleagues (1970) and in more detail by Edelstone and colleagues (1978) by using the isotope-labelled microsphere method. This preferential streaming could explain the early observation of Barcroft (1946) that in fetal lambs carotid arterial blood has a higher oxygen saturation of haemoglobin than femoral arterial blood. The preferential streaming of umbilical venous blood to the upper body segment implies that any substance that enters the umbilical vein, e.g. glucose (Charlton & Johengen, 1987) and drugs administered to the mother, will be delivered to the heart and brain in higher concentrations (Rudolph, Itskovitz, Iwamoto, Reuss & Heymann, 1981).

The distribution of cardiac output in the fetus during normoxemia

The normal range of blood gases, acid-base balance, physiologic variables, combined ventricular output, and umbilical blood flow in chronically prepared fetal sheep near term observed by various groups is given in Table 1. In resting fetal sheep at 0.85 of pregnancy (3-4 days after surgery) mean heart rate is 170 beats/min, arterial blood pressure is 44mmHg, ascending aortic pH is 7.40, PO_2 is 24 mmHg, PCO_2 is 47mmHg, oxygen saturation of haemoglobin is 67%, haemoglobin is 8.6 g/dl, and oxygen content is 7.8 ml/dl (Jensen *et al.*, 1991). The corresponding values of samples withdrawn simultaneously from various major fetal vessels, including descending aorta, umbilical vein, abdominal inferior vena cava, superior vena cava, and superior sagittal sinus, are presented elsewhere (Jensen *et al.*, 1991). The values of umbilical venous, ascending and descending aortic oxygen saturation determined in the chronic model are in remarkable agreement with those from acutely instrumented fetal sheep published by Dawes, Mott & Widdicombe (1954).

Under physiologic conditions, as reflected by these blood gas values, the combined ventricular output (cardiac output) at 0.9 gestation is approximately 480 ml/min/kg fetal weight. Its distribution to the principal fetal organs during normoxemia, the resulting blood flow and O_2 delivery, and the vascular resistances are presented elsewhere (Itskovitz *et al.*, 1987; Jensen *et al.*, 1991). About 55% of the cardiac output are

Table 1. Normal blood gases in chronically-prepared fetal sheep.

Gestational age (days)	123–140[a]	131–141[b]	123–130[c]	130–145[d]	120–126[e]	123–129[f]
pH	7.35 ± 0.01	7.37 ± 0.01	7.40 ± 0.04	7.33 ± 0.02	7.36 ± 0.01	7.40 ± 0.01
PO_2 (mmHg)	21.9 ± 0.7	22.0 ± 1.0	20.0 ± 3.0	20.6 ± 0.8	21.4 ± 0.9	24.1 ± 2.4
PCO_2 (mmHg)	42.5 ± 1.3	42.0 ± 1.0	46.0 ± 5.0	49.8 ± 1.5	46.0 ± 0.9	47.3 ± 3.9
Heart rate (beats/min)	174 ± 4	–	165 ± 24	163 ± 5	169 ± 10	167 ± 19
Blood pressure (mmHg)	47 ± 2	–	42 ± 5	45.9 ± 1.2	48 ± 4	44.2 ± 3.5
Cardiac output (ml x min^{-1} x kg^{-1})	474 ± 35	–	450 ± 69	592 ± 28	528 ± 43	478 ± 94
Umbilical blood flow (ml x min^{-1} x kg^{-1})	190 ± 18	–	188 ± 55	90 ± 10†	214 ± 23	213 ± 55

† ml x min^{-1} x $100g^{-1}$
Data is taken from [a] Iwamoto *et al.*, 1979; [b] Robillard *et al.*, 1981 ;[c] Reuss *et al.*, 1982;[d] Gilbert, 1980; [e] Court *et al.*, 1984; [f] Jensen *et al.*, 1991

distributed to the fetal body and 45% to the placenta. About 30% are directed to the fetal carcass, which includes skeletal, muscle, bones, skin, and connective tissues, and 11% to the lungs. During normoxemia only small fractions of the cardiac output are distributed to the brain (3%), heart (2.6%), small gut (2.6%), kidneys (2.3%), and adrenals (0.006%) (Jensen *et al.*, 1991). With regard to oxygen requirements it is noteworthy that in the human fetus cerebral blood flow comprises a larger fraction of the cardiac output, because the brain/body weight ratio is higher than in sheep.

This normal distribution of blood flow changes dramatically in late gestation during hypoxemia and even more so during asphyxia. The following sections will describe the general changes in the distribution of fetal organ blood flows when oxygen is at short supply. The effect of various experimental interventions that result in fetal hypoxemia and a redistribution of blood flow and oxygen delivery will be emphasized. Table 2 summarizes the results of some significant studies on changes in blood gas tensions and organ blood flows.

Cardiovascular responses to oxygen lack induced by various methods.

Effects of maternal hypoxemia

Maternal hypoxemia is usually produced by manipulating the inspired fraction of oxygen, to reduce maternal arterial PO_2 to about 40 mmHg. This results in fetal arterial PO_2 values of about 10–12 mmHg. Due to hyperventilation of the ewe, fetal blood PCO_2 falls, too. To study the effects of isocapnic hypoxemia on the fetal circulation, it is necessary to increase carbon dioxide concentrations in the inspired gas mixture ($FiCO_2$ = 3–4 %).

The resulting moderate fetal hypoxemia (arterial PO_2 = 10–12 mmHg) causes a fall in heart rate and an increase in arterial blood pressure (Cohn *et al.*, 1974), but combined ventricular output, measured by injecting isotope-labelled microspheres into the fetal circulation (Rudolph & Heymann, 1967), does not fall as long as blood pH is maintained. Only when hypoxemia is accompanied by acidemia cardiac output falls by about 20% (Cohn *et al.*, 1974). Umbilical blood flow is maintained, while blood flow to the fetal body is reduced by 40% (Cohn *et al.*, 1974; Parer, 1980).

The distribution of the combined ventricular output changes in the fetus much the way it does in the adult. There is circulatory centralization of blood flow in favour of the brain, heart, and adrenals, and at the expense of peripheral organs, including lungs, kidneys, gastrointestinal tract, and carcass (Fig. 1) (Campbell *et al.*, 1967; Cohn *et al.*, 1974; Peeters *et al.*, 1979, Ashwal *et al.*, 1981). This holds true for normally grown and growth retarded fetuses.

Fetal hypoxemia is also accompanied by a redistribution of umbilical venous blood flow. The fraction of blood by-passing the liver through the ductus venosus increases from 55% to 65% (Reuss & Rudolph, 1980; Edelstone *et al.*, 1980), thus contributing considerably to the maintenance of oxygen delivery to the fetus. In addition, there is a preferential streaming of umbilical venosus blood across the foramen ovale via the left ventricle towards the upper body circulation to maintain oxygen delivery to the heart and brain (Reuss & Rudolph, 1980)

During fetal hypoxemia the proportion of superior vena cava blood flow directed through the foramen ovale into the upper body segment is slightly increased (Cohn *et al.*, 1974).

During hypoxemia the venous blood returning to the heart via the abdominal vena cava inferior is reduced by 50%. Thus, the blood returning from umbilical vein, superior vena cava and inferior vena cava contribute 32%, 30% and 44% to placental blood flow, respectively and hence recirculate to the fetus via the umbilical vein (Reuss & Rudolph, 1980).

In summary, during moderate hypoxemia cardiac output is maintained (unlike hypoxemia plus acidemia) and the circulating blood is redistributed to the brain, heart, and adrenals at the expense of peripheral organs, including the lungs. This circulatory centralization is accompanied by a changing pattern of venous return and by a preferential streaming of umbilical venous blood through the ductus venosus and the foramen ovale to the upper body segment.

Reduction in umbilical blood flow

Reduction in umbilical and placental blood flow can be

Table 2. Fetal changes during hypoxaemia and asphyxia.

	Cohn et al., 1974 122–142 days Maternal hypoxaemia (FiO_2)		Jensen et al., 1987b 130 ± 2 days Arrest of uterine and ovarian blood flow (4 min)	Itskovitz et al., 1987 119–123 days Reduction of umbilical blood flow by 50%
	without acidaemia	with acidaemia		
Heart rate (beats/min)	164->122	160->113	170->80	177->152
Arterial blood pressure (mmHg)	57->65	63->76	55->70	44->49
pH	7.37->7.36	7.36->7.26	7.30->7.05	7.39->7.36
PO_2 (mmHg)	19->11	20->12	19->6	23->18
PCO_2 (mmHg)	42->42	44->43	50->86	43->46
		Blood flow changes		
Umbilical cord (ml/min/kg)	191->213	195->205	311->151 †	233->115
Fetal body (ml/min/kg)	273->229	302->177	164->55 °†	278->302
Brain	96->168	120->185	194->144	112->160
Heart	179->449	185->482	261->380	197->277
Adrenal	271->828	302->855	437->941	217->436
Liver arterial	–	–	21->8	13->10
Kidney	175->136	162->81	253->23	154->174
Lungs	60->27	57->32	75->30	131->65
Gastrointestinal tract	67->53a	96->41a	179->21 b 110->8 c	82->100 a
Carcass	20->14	20->6	–	21->25
Muscle	–	–	17->0.8	–
Skin	–	–	32->1.3	–

	Block et al., 1990a 124–132 days Arrest of uterine blood flow plus maternal hypoxemia		Jensen et al., 1991 123–129 days Graded reduction of uterine blood flow	Toubas et al., 1981 100–147 days Reduction in fetal blood volume by 15%
	Hypoxaemia with severe acidaemia	Agonal heart rate pattern	Graded reduction of uterine blood flow*	Reduction in fetal blood volume by 15%
Heart rate (beats/min)	161->105	161-> 81	167->140	186->151
Arterial blood pressure (mmHg)	51->43	51->25	44->53	51->46
pH	7.32->7.00	7.32->6.86	7.40->7.25	7.39->7.30
PO_2 (mmHg)	23->4	23->2.3	24->16	23.7->23.5
PCO_2 (mmHg)	51->90	51->111	47->60	39.7->44.1
		Blood flow changes		
Umbilical cord (ml/min/kg)	158->67	158->7	213->209	264->191
Fetal body (ml/min/kg)	428->187	428->55	315->247	340->252
Brain	158->185	158->7	88->154	84->99
Heart	252->597	252->28	163->368	195->169
Adrenal	314->545	314->79	174->657	375->437
Liver arterial	–	–	–	7.6->9.1
Kidney	134->75	134->4	155->107	246->187
Lungs	–	–	162->106	129->60
Gastrointestinal tract	–	–	90->62 b 41->35 c	55->47
Carcass	39->12	39->5	21->13	26->17
Muscle	–	–	–	–
Skin	–	–	–	–

* To effect a reduction in fetal oxygen delivery by 50%; a = gut; b = small gut; c = large gut; ° excluding carcass; † (ml/min/100g)

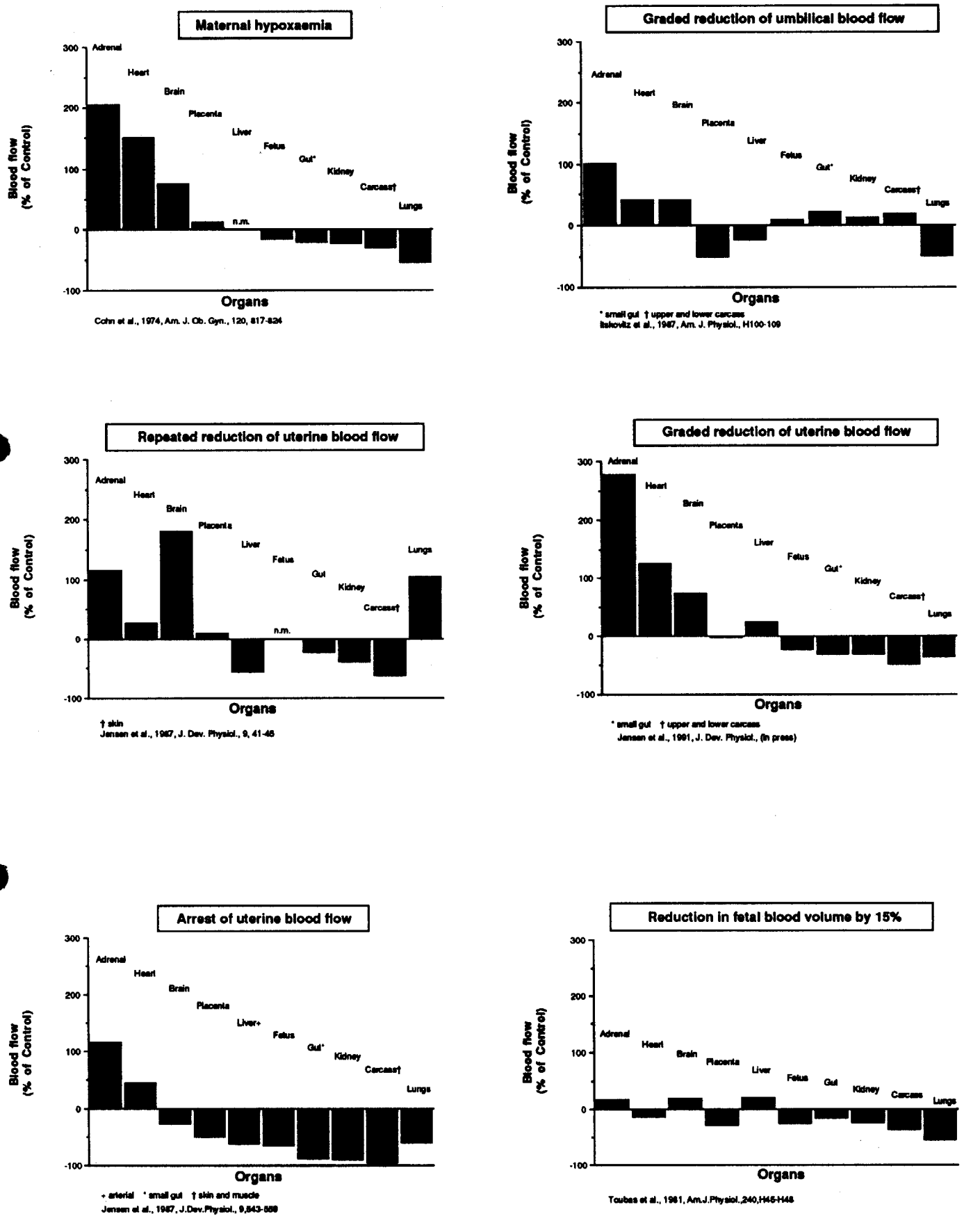

Fig. 1. Redistribution of organ blood flow (% of control) in chronically prepared fetal sheep near term during various experimental perturbations.

achieved by compression of the umbilical vein (Künzel *et al.*, 1977), compression of the fetal abdominal aorta (Edelstone *et al.*, 1980), by snaring the umbilical cord (Itskovitz *et al.*, 1983a, 1983b, 1987), and by an embolization of the placental vascular bed (Clapp *et al.*, 1981, Trudinger *et al.*, 1987).

A reduction of arterial and/or venous umbilical blood flow causes a decrease in oxygen delivered to the fetus. Unlike during maternal hypoxemia, this does not decrease umbilical venous oxygen content (Künzel *et al.*, 1977), Itskovitz *et al.*, 1987). Therefore, a reduction in umbilical blood flow, e.g. by 50%, results in a similar reduction in oxygen delivery to the fetus (Itskovitz *et al.*, 1983b).

Due to the favourable relationship between uterine and umbilical blood flow, umbilical venous PCO_2 does not change, and fetal arterial blood pH does not change even though umbilical blood flow and hence fetal oxygen delivery is reduced to 50% of normal.

A compression of the umbilical cord is accompanied by an increase in arterial blood pressure, a fall in heart rate, and a fall in combined ventricular output (Künzel *et al.*, 1977, Itskovitz *et al.*, 1982a, 1983a, 1983b, 1987).

Reduced umbilical blood flow is accompanied by a redistribution of blood flow to the fetal organs that is different from that observed during maternal hypoxemia (Fig. 1). Blood flows to the brain (+43%), heart (+41%) and adrenals (+100%) increase. However, unlike during maternal hypoxemia, blood flows to the peripheral organs, including those to the kidney, gastrointestinal tract, and spleen do not change, and that to the carcass increases (+20%). Only blood flow to the lungs falls (-50%).

The fraction of umbilical blood flow shunted through the ductus venosus increases by 30% when umbilical blood flow is reduced by 75% (Edelstone *et al.*, 1980). However, the proportion of venous return from both inferior and superior vena cava increase relative to that from the umbilical vein. Therefore, the oxygen content of the blood crossing the foramen ovale falls and oxygen delivery to the brain and heart is maintained by increasing blood flow (Itskovitz *et al.*, 1987).

Reduction in uterine blood flow

Uterine blood flow can be reduced by various methods, including compression of the maternal aorta (Wilkening & Meschia, 1983; Jensen *et al.*, 1985b, 1987a,b,c,d), the uterine arteries (Yaffe *et al.*, 1987) or the uterine veins (Künzel *et al.*, 1975, Lotgering & Wallenburg, 1986) or by embolization of the uterine vascular bed (Creasy *et al.*, 1973).

The hemodynamic effects of reduced uterine blood flow depend largely on the severity of the reduction. The most severe insult of course is arrest of uterine blood flow that interrupts both materno-fetal oxygen delivery and feto-maternal carbon dioxide clearance. Due to collateral blood supply to the sheep uterus including that provided by the ovarian arteries, arrest of uterine blood flow can only be achieved by complete compression of the abdominal maternal aorta below the renal arteries.

Graded reduction in uterine blood flow

Graded reduction in uterine blood flow to achieve a fall in fetal oxygen delivery by 50% and a final carotid arterial PO_2 of 16 mmHg is associated with fetal bradycardia of mild degree and an increase in fetal aortic pressure (Skillman *et al.*, 1985; Jensen *et al.*, 1991). These changes are similar to those occurring during maternal hypoxemia and with umbilical cord compression, but of different degree. Also, whereas combined ventricular output decreases during cord compression, it does not change significantly with graded uterine blood flow reduction (Jensen *et al.*, 1991).

The redistribution of cardiac output and of blood flow to individual organs during graded reduction of uterine blood flow is qualitatively similar, but quantitatively different from that observed during arrest of uterine blood flow (Fig. 1). Blood flow to the brain, heart, and adrenals increase and those to the carcass and to the skin fall, while umbilical blood flow is maintained (Jensen *et al.*, 1991). If arterial PO_2 falls below 14 mmHg, umbilical blood flow falls (Cohn *et al.*, 1985).

During graded reduction in uterine blood flow umbilical venous blood directed through the ductus venosus increases, as does the fraction of umbilical venous blood crossing the foramen ovale. There is a significant increase in blood returning from both superior and abdominal inferior vena cava and from the umbilical vein via the ductus venosus that crosses the foramen ovale to the upper body segment. However, due to the oxygen content that is higher in the umbilical venous and in the superior vena cava blood than in the abdominal inferior vena cava blood, the relative contribution to the oxygen delivered to the heart and brain by blood derived from the former veins is much higher than that contributed by the abdominal vena cava (Jensen *et al.*, 1991).

Repeated brief arrest of uterine blood flow

Repeated reductions in uterine blood flow occur quite frequently during the second stage of labour and expose the fetus to various degrees of distress. In spite of its clinical relevance there are only a few systematic studies devoted to this particular mode of repeated restriction of oxygen delivery to the fetus. One of these studies tried to mimic changes in the uterine vascular bed in the second stage of labour by repeatedly inflating a balloon catheter, which was advanced into the abdominal maternal aorta (Jensen *et al.*, 1985a), in an acute fetal sheep model. Uterine blood flow was intermittently arrested 11 times within 33 minutes. Each single asphyxial episode lasted 30, 60 or 90 seconds. Depending on the duration of asphyxia there is a repeated fall in arterial oxygen saturation of haemoglobin, heart rate, skin blood flow and

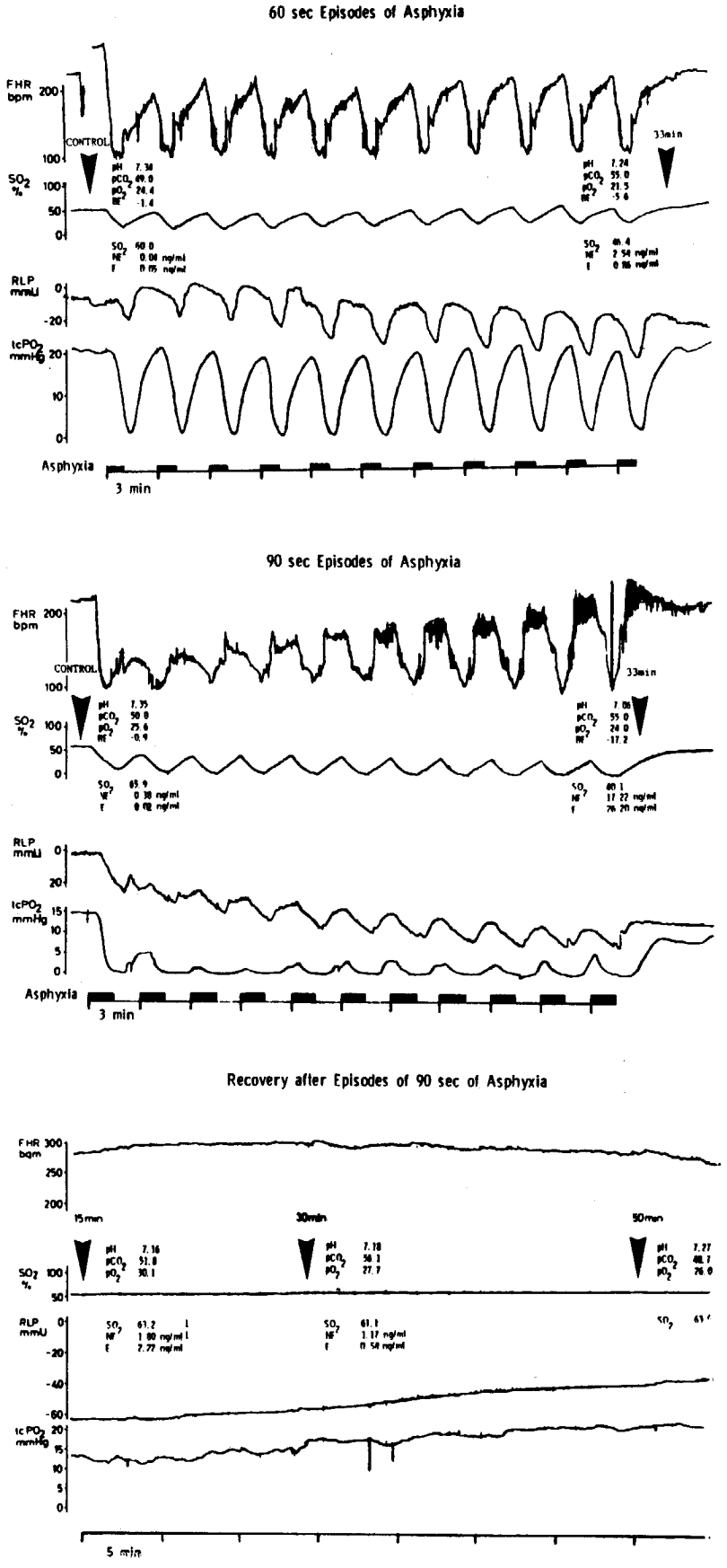

Fig. 2. Repeated brief arrest of uterine blood flow for 60s and 90s in acutely prepared fetal sheep near term. Original recordings of (from the top) fetal heart rate, oxygen saturation (SO_2), skin perfusion (mm units deflection) and transcutaneous PO_2. Note: In contrast to 60 seconds, arrest of uterine blood flow for 90 seconds suppresses the transcutaneous PO_2 signal, although O_2 saturation returns to normal. This is due to increasing catecholamine concentrations that reduce skin blood flow during repeated asphyxia. After asphyxia (bottom) oxygen saturation of haemoglobin is high and all variables recover. With decreasing catecholamine concentrations blood flow to the skin, transcutaneous PO_2, and heart rate return to normal (Jensen *et al.*, 1985a).

transcutaneously measured PO_2 ($tcPO_2$), whereas arterial blood pressure and plasma catecholamine concentrations rise (Jensen *et al.*, 1985a) (Fig. 2). With increasing duration of repeated arrest of uterine blood flow fetal skin blood flow decreases to such an extent that the transcutaneous PO_2 signal is suppressed even though central oxygenation is restored. This suggests that in the presence of fetal bradycardia, low transcutaneous PO_2 readings may be used as an index of poor skin blood flow and hence of a circulatory redistribution (Fig. 2), as proposed previously (Jensen & Künzel, 1980). This view is supported by close correlations between fetal skin blood flow and plasma catecholamine concentrations (Jensen *et al.*, 1987c).

The observation that reduced blood flow to the fetal skin during repeated reduction in uterine blood flow can be detected by transcutaneous PO_2-measurements, has been confirmed by studies, in which microspheres were injected into the fetal circulation (Jensen *et al.*, 1987a). These studies showed that reduced skin blood flow is accompanied by both increased sympathetic activity, as assessed by plasma catecholamine concentrations, and a redistribution of systemic blood flow (Fig. 1). This may be of clinical significance, because early detection of fetal circulatory centralization through variables that depend on skin blood flow may improve fetal surveillance during complicated labour (Jensen & Künzel, 1980; Paulick, Kastendieck & Wernze, 1985; Jensen *et al.*, 1985a, 1987a,c).

The pattern of redistribution of fetal blood flow after repeated brief episodes of asphyxia, caused by arrest of uterine blood flow for 90 sec, is different from that during prolonged asphyxia or maternal hypoxemia. Myocardial blood flow, for instance, which increases during various interventions (Campbell *et al.*, 1967; Cohn *et al., 1974;* Peeters *et al.*, 1979; Fisher *et al.*, 1982a, 1982b; Itskovitz *et al.*, 1987; Jensen *et al.*, 1991) was not increased significantly 4 minutes after the last asphyxial episode. This suggests that increased myocardial flows recover more rapidly after repeated than after prolonged asphyxia (Fig. 1).

Another difference is that blood flow to the lungs increases under these experimental conditions (Fig. 1). This may be related to either vasodilatation in the lungs or to increased arterial pressure in the pulmonary artery due to a transient constriction of the ductus arteriosus (Jensen *et al.*, 1987a).

Prolonged arrest uterine blood flow

Prolonged arrest of uterine blood flow for 4 minutes causes severe fetal asphyxia. Heart rate, arterial oxygen content, pH, and combined ventricular output fall, and arterial blood pressure, PCO_2, and lactate concentrations rise rapidly (Jensen *et al.*, 1987b).

This acute severe asphyxia is accompanied by rapid changes in both the fetal and the umbilical circulation. To study the changes in organ blood flow distribution at short intervals a modification of the isotope labelled microsphere method has been devised, in which microspheres are injected serially during continuous withdrawal of the reference blood samples (Jensen *et al.*, 1987b). The redistribution of cardiac output is qualitatively similar to that observed during graded reduction in uterine blood flow and during maternal hypoxemia, in that the fractions of cardiac output distributed to the brain, heart, and adrenals increase, while those to peripheral organs fall drastically (Fig. 1). However, there are distinct differences, for example cardiac output falls markedly. Furthermore, there are differences in actual cerebral vascular resistance and in both blood flow and oxygen delivery to the brain, in that cerebral blood flow does not rise. Thus, oxygen delivery to the cerebrum falls whereas that to the brainstem is maintained, reflecting a redistribution of brain blood flow in favour of brainstem areas (Fig. 1) (Jensen *et al.*, 1987b).

If severe asphyxia caused by arrest of uterine blood flow is prolonged, circulatory centralization cannot be maintained (Fig. 3). Rather, there is a decentralization with a decrease in vascular resistance in peripheral organs and an increase in resistance in central organs, including those in the brain and the heart. Also umbilical resistance rises and hence placental blood flow falls. These changes, which are associated with severe metabolic derangements and severe acidemia below pH 7.0, will lead to fetal demise, unless immediate resuscitation occurs (Jensen *et al.*, 1987b; Block *et al.*, 1990a).

During decentralization at the nadir of asphyxia (Fig. 3), the loss of peripheral vascular resistance may be related to the severity of local acidosis causing the

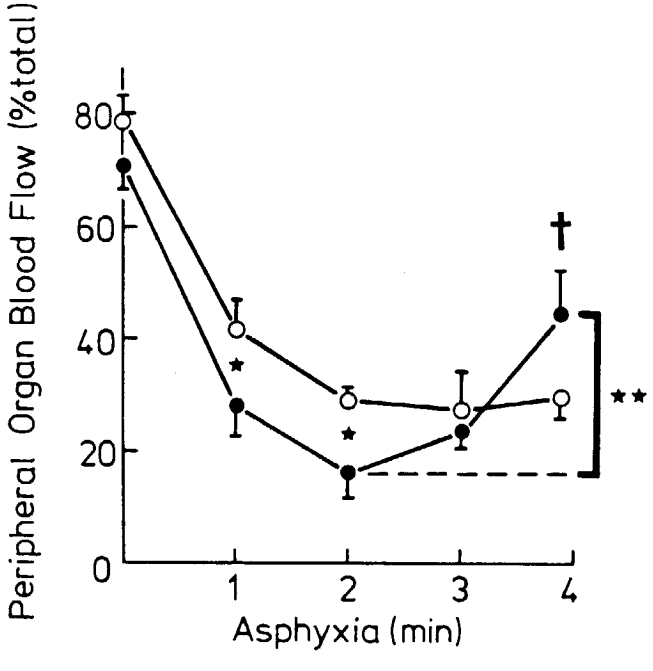

Fig. 3. Changes in blood flow to peripheral organs during acute asphyxia in 4 surviving (o) and 5 non-surviving (•) fetal sheep near term. Note, that, unlike in surviving fetuses, at the nadir of asphyxia (at 4 min) in non-surviving fetuses, the proportion of blood flow directed to peripheral organs was significantly higher than at 2 min of asphyxia (**, P=0.01; 2 min vs. 4 min) Jensen *et al.*, 1987b.

vascular smooth muscle in peripheral arteries to dilate (Jensen, Gips, Hohmann, Künzel, 1988). The fate of the fetus during severe asphyxia is determined by the degree of hypoxic myocardial depression and by the depletion of cardiac glycogen stores. Agonal heart rate patterns, increasing degree of cardiac failure and the resulting increase in central venous pressures precede fetal death (Block *et al.*, 1990a)

There is one report on fetal circulatory derangements during reduction of blood flow through common hypogastric artery by 75% leaving ovarian anastomoses intact. In that study cardiac output and umbilical blood flow were maintained. However, an increase in vascular resistance in the brain and heart was observed. The fact that these changes occurred during moderate acidemia (pH 7.14 ± 0.02) and the fact that these changes were accompanied by only minor reductions in peripheral blood flows renders these results difficult to interpret (Yaffe *et al.*, 1987).

Fetal haemorrhage

A reduction in fetal oxygen delivery can also be produced by reduction in fetal blood volume, i.e. anaemic hypoxemia (Mac Donald *et al.*, 1980; Toubas *et al.*, 1981; Itskovitz et al., 1982b). A fall in blood volume by 15-20% is accompanied by a reduction in heart rate (-20%), arterial blood pressure (-10%), and cardiac output (-25%).

The resulting redistribution of fetal organ blood flow is different to that observed during hypoxemia and asphyxia (Fig. 1), in that blood flows to the heart, brain and adrenals are maintained, but not increased. Blood flows to almost all peripheral organs and that to the placenta fall (Toubas *et al.*, 1981; Itskovitz *et al.*, 1982b).

The fraction of umbilical venous blood passing through the ductus venosus increases and contributes about 30% to the cardiac output. Hence, ductus venosus derived blood flow and oxygen delivery to the upper and lower body segments increase also by 30% (Itskovitz *et al.*, 1982b). Prolonged but quantitatively similar volume losses, e.g. 30% over a period of 2 hours, cause less pronounced changes in the cardiovascular variables changes (Brace & Cheung, 1986).

Chronic hypoxemia

A number of experimental models have been devised in sheep, guinea pigs and rats to produce chronic fetal hypoxemia with consecutive intrauterine growth retardation. These include prolonged maternal hypoxemia (Gilbert *et al.*, 1979; Jacobs *et al.*, 1988; Kitanaka *et al.*, 1989), reduction of placental size by preconceptional removal of endometrial caruncles (Alexander, 1964; Robinson *et al.*, 1979), placental damage by embolization of the utero-placental bed (Creasy *et al.*, 1973; Clapp *et al.*, 1981; Charlton & Johengen, 1987), embolization of the fetal placental vascular bed (Trudinger *et al.*, 1987, Block *et al.*, 1990a), ligation of uterine (Wigglesworth, 1964; Lafeber *et al.*, 1979; Lafeber *et al.*, 1984) or umbilical arteries (Emmanoulides *et al.*, 1968), and maternal heat stress (Alexander *et al.*, 1987). However, fetal growth retardation can also be produced by substrate restriction without any apparent changes in fetal oxygen delivery (Charlton & Johengen, 1985, Mellor, 1983).

All of these perturbations are associated with a decrease in placental size and/or transfer function that is directly related to the magnitude of retardation in fetal growth (see Clapp, 1988, for review). The actual mechanisms involved in reduction of fetal growth are not well understood. However, there is clear evidence for oxygen lack to be one important factor. But there are also structurally unknown placental signals to consider that might initiate the cessation of fetal growth before a relevant hypoxemia occurs (Jones, 1985). Thus, placental membranes play an important part in the production of prostaglandins, particularly that of prostacyclin (PGI_2) one of the most potent vasodilators (Lewis *et al.*, 1983; Mitchell *et al.*, 1978). There is for instance a substantial reduction in prostacyclin production in placentae of fetuses that are chronically hypoxaemic and growth retarded (Jogee *et al.*, 1983). Whether this reduction in prostacyclin concentrations is related to an elevated vascular resistance in the fetus is at present unclear.

Reduced fetal growth is associated with a number of metabolic and endocrine changes including hypoglycaemia, hypoinsulinaemia, increase concentrations of glucagon, lactate, alanine, triglycerides (see Robinson *et al.*, 1985 for review), cortisol (Clapp *et al.*, 1982), catecholamines, β-endorphins and decreased concentrations of growth-promoting factors, i.e. T3, T4, somatomedins and prolactin. ACTH, insulin like growth factor (IGF-2), ovine placental lactogen and growth hormone are unchanged (Robinson et al., 1985; Clapp, 1988; Jones *et al.*, 1987, 1988a).

The consumption of oxygen and glucose by the fetus are reduced in absolute terms, but are maintained in terms of fetal body mass (Owens *et al.*, 1987a,b). However, the utero-placental consumption of glucose per weight of placenta is reduced and a greater proportion of that glucose or other substrates are converted to lactate by the placenta. And there is also an increase in the fraction of lactate produced by utero-placental tissues that is secreted into the fetal circulation (Owens *et al.*, 1987b).

Growth retarded fetuses tend to have a lower arterial blood pressure and a higher heart rate under control conditions (Robinson *et al.*, 1983) (Fig. 4). The chronic reduction in fetal oxygen delivery is compensated in part by an increased packed cell volume with an increased transport capacity for oxygen (Robinson *et al.*, 1983; Jacobs *et al.*, 1988).

Minor degrees of chronically reduced fetal oxygen delivery are not necessarily associated with major circulatory responses (Block *et al.*, 1990b). However, major changes in chronically reduced fetal oxygen

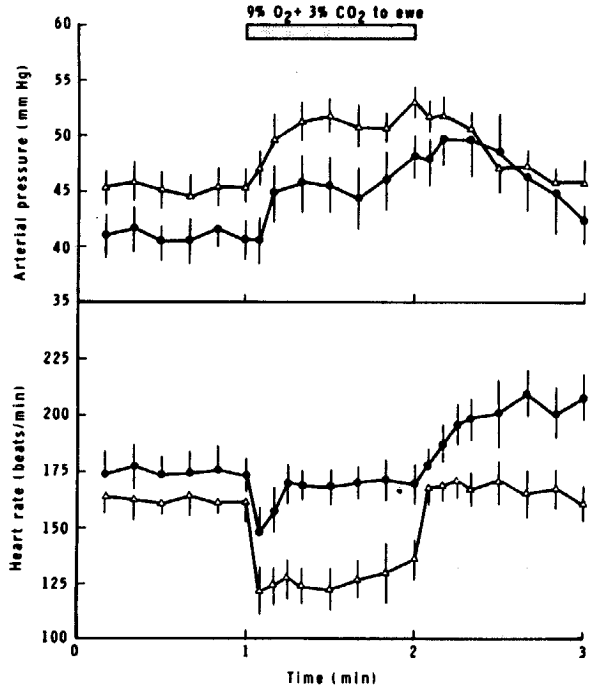

Fig. 4. The diagram shows the changes in blood pressure and heart rate in fetal sheep during maternal hypoxemia (FiO_2=9%). Note that in the growth retarded fetuses (•) blood pressure in lower and heart rate is higher than in the normal fetuses (from Robinson *et al.*, 1983).

delivery cause a circulatory centralization in favour of the brain and heart (Creasy *et al.*, 1973). This is reflected by a relative maintenance of the weight of central organs as compared to that of the fetal body in general and the fetal liver in particular. Therefore, it has been suggested to use the brain/liver weight ratio as an index of fetal growth retardation (Jones *et al.*, 1987). The responses of growth retarded fetuses to acute hypoxemia or asphyxia is different from that observed in normal-sized fetuses, in that they develop acidemia more easily. Furthermore, bradycardia is brief and heart rate returns to control values quickly after the onset of acute hypoxemia (Robinson *et al.*, 1983), whereas tachycardia develops during recovery. This has been attributed to an increased sympathetic tone in growth retarded fetuses (Jones & Robinson, 1975; Llanos *et al.*, 1980), even though their adrenaline responses to hypoxemia are not particularly high (Jones & Robinson, 1983).

During hypoxemia in growth retarded fetuses there is only a small increase in plasma glucose concentrations that may be due to failure to mobilize glycogen stores. This is accompanied by only a small decrease in insulin concentrations (Robinson *et al.*, 1983), that may be explained by the fact that basal glucose concentrations in the fetal plasma are poor and cannot be reduced further, because the reduction of peripheral glucose consumption is limited.

There is also evidence for an activation of the pituitary-adrenal axis in growth retarded fetuses, because both plasma ACTH- and cortisol concentrations are substantially higher during hypoxemia than in normal sized fetuses (Robinson *et al.*, 1983). This may be related to the induction of preterm labour (Challis *et al.*, 1984; Liggins & Schellenberg, 1988).

Circulatory changes during oxygen lack in immature fetuses

The knowledge on circulatory changes during oxygen lack in immature fetuses is scarce. However, it is clear from the existing reports that there are distinct differences between immature and mature fetuses. In general, during normoxaemia heart rate is higher and arterial blood pressure is lower in immature than in mature fetuses, and combined ventricular output increases throughout gestation in proportion to fetal growth (Rudolph & Heymann, 1970). Furthermore, as far as the circulatory response to hypoxia or asphyxia during development is concerned, there appears to be a different balance of parasympathetic and sympathetic control of the fetal heart rate early in gestation, so that heart rate does not fall or even increases during maternal hypoxemia (Walker, Cannata, Dowling, Ritchie & Maloney, 1978, 1979).

There is only one systematic study available on the circulatory effects of maternal hypoxemia on immature, i.e. 0.7 gestation; and very immature, i.e. 0.6 gestation, chronically prepared fetal sheep (Iwamoto, Kaufman, Keil & Rudolph, 1989a; Iwamoto, 1989b). These authors examined in detail the changes of heart rate, arterial blood pressure, distribution of cardiac output, organ blood flows and vascular resistance during moderate hypoxemia, i.e. 12–14 mmHg PO_2 in the descending fetal aorta. Under these conditions, which were accompanied by slight fetal acidemia, arterial blood pressure and heart rate did not change at 0.6 gestation. Whereas heart rate increased significantly at 0.7 gestation (Table 3). As in mature fetuses, cerebral, myocardial, and adrenal blood flows, measured by the microsphere method (Rudolph & Heymann, 1967), increased, and pulmonary blood flow decreased. The authors conclude that these responses mature early and are likely to be local vascular responses to decreases in oxygen content (Iwamoto *et al.*, 1989a). Furthermore, they found that combined ventricular output and umbilical-placental blood flow decreased in both groups (Table 3). Interestingly, in the very immature fetuses, there was no change in blood flow to the carcass, i.e. musculo-skeletal and cutaneous circulations, gastrointestinal or renal circulations during hypoxemia, whereas blood flow to the carcass fell in the immature fetuses, suggesting that peripheral vasomotor control starts to develop at approximately 0.7 gestation. This, among other vasoactive substances may also involve arginine-vasopressin, which was increased at 0.7 gestation. But these differences in responses between 0.6 and 0.7 gestation may also indicate immaturity in chemoreceptor function, in response of neuro-hormonal modulators, or in response of regional receptor effect or mechanisms (Iwamoto *et al.*, 1989a).

Only recently, comparative information on the effects of acute asphyxia, caused by arrest of uterine

Table 3. Effect of acute hypoxemia on heart rate, arterial blood pressure, and blood flow in young fetal sheep.

Mean gestational age	88 days		98 days		135 days*	
	Control	Hypoxemia	Control	Hypoxemia	Control	Hypoxemia
Heart rate (beats/min)	224 ± 27	237 ± 35	203 ± 16	226 ± 19†	160 ± 9	113 ± 27†
Arterial blood pressure (torr)	31 ± 6	30 ± 7	40 ± 3	39 ± 3	63 ± 7	76 ± 13‡
Blood flow ($ml \cdot min^{-1} \cdot kg^{-1}$)						
Combined ventricular output	516 ± 95	445 ± 75	566 ± 65	425 ± 148†	497 ± 58	381 ± 38†
Umbilical-placental	256 ± 81	163 ± 54‡	300 ± 69	197 ± 65§	195 ± 54	205 ± 56
Fetal body	261 ± 34	282 ± 50	266 ± 36	228 ± 93	302 ± 42	177 ± 38†
Vascular resistance ($torr \cdot ml \cdot min^{-1} \cdot kg^{-1}$)						
Total	0.06 ± 0.02	0.07 ± 0.02	0.07 ± 0.01	0.10 ± 0.03	NA	NA
Umbilical-placental	0.13 ± 0.05	0.22 ± 0.13	0.14 ± 0.04	0.20 ± 0.07†	NA	NA
Fetal body	0.12 ± 0.03	0.11 ± 0.04	0.16 ± 0.03	0.19 ± 0.08	NA	NA

Values were expressed as mean ± SD. * data derived from [14] with modification; † $P<0.05$; ‡ $P<0.01$; § $P<0.005$: significantly different from control value, paried t-test. NA = not available (Iwamoto, 1989).

blood flow on chronically prepared fetal sheep at 0.6, 0.75 and 0.9 gestation have become available (Jensen 1991). Under these conditions, heart rate falls during and recovers after asphyxia in all age groups (Fig. 5). However, there are major differences in the arterial blood pressure, which is significantly poorer at 0.6 than at 0.75 and 0.9 gestation. During one and two minute asphyxia arterial blood pressure does not change significantly at 0.6, rises after a transient decrease at 0.75 and progressively rises at 0.9 gestation (Fig. 5). These responses are accompanied by age-dependent changes in plasma concentrations of epinephrine and norepinephrine. Epinephrine concentrations do not change significantly and increase in concentration of norepinephrine is blunted during asphyxia at 0.6 gestation, whereas high and extremely high plasma concentrations can be measured at 0.75 and 0.9 gestation, respectively.

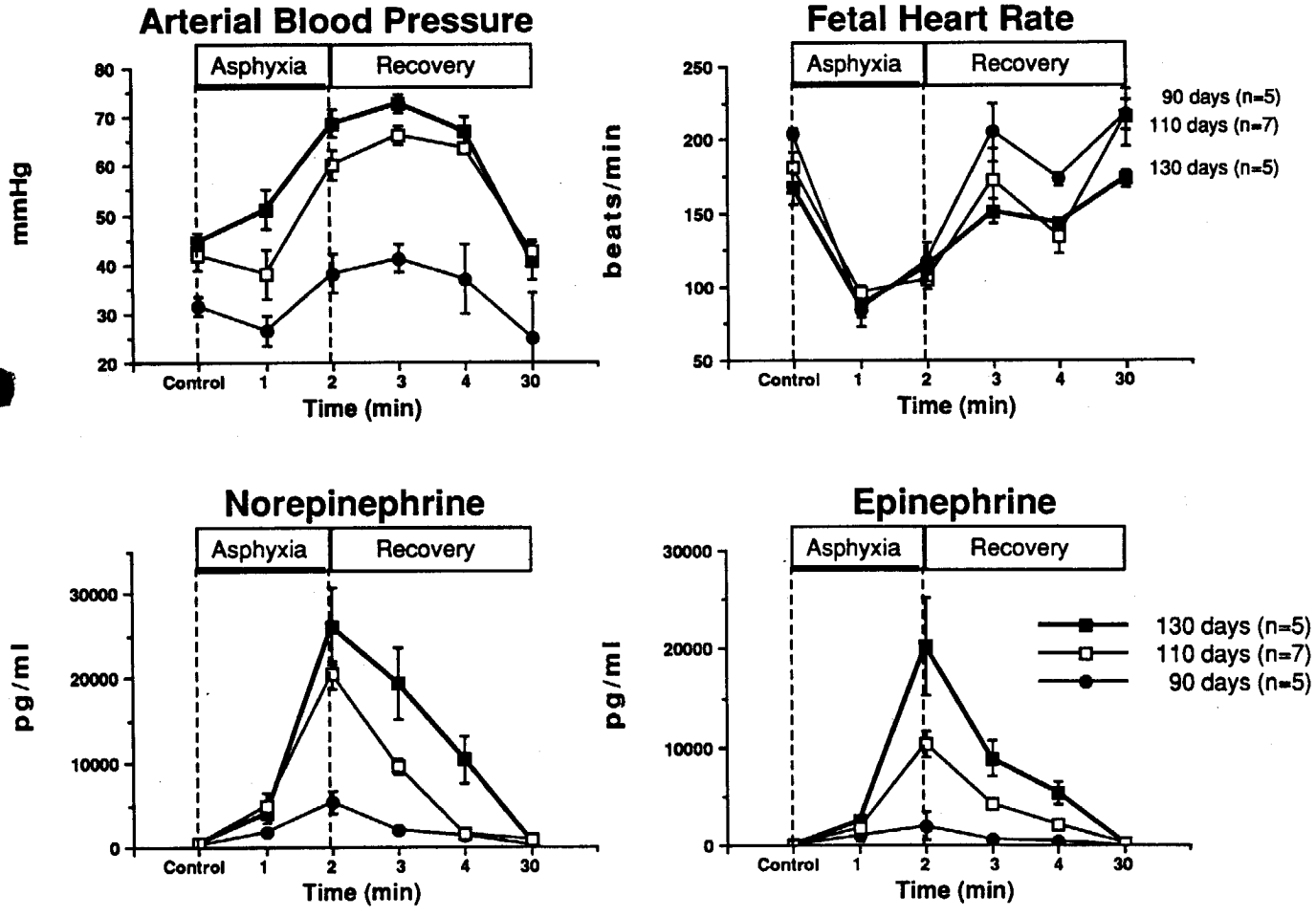

Fig. 5. Changes in arterial blood pressure, heart rate, norepinephrine, and epinephrine concentrations during arrest of uterine blood flow for 2 minutes in chronically prepared fetal sheep at 0.6, 0.75, 0.9 gestation (Jensen, 1991).

There are also age-dependent differences in organ blood flow. For example, blood flow to the brain per 100 g is lowest, higher and highest at 0.6, 0.75 and 0.9 gestation, respectively (Jensen, 1991). Interestingly during recovery in the youngest group of fetuses, there is a steady increase in blood flow to all parts of the brain, including the germinal matrix. Whether this may be related to the well known-fact that cerebral haemorrhage, which in immature human fetuses originates from the germinal matrix in 80% of the cases, remains to be established.

Blood flow to the myocardium increases progressively during asphyxia without differences between age groups and recovers thereafter in the fetuses at 0.75 and 0.9 gestation. Only in the youngest group of fetuses there is an increase in myocardial blood flow in the late recovery period, suggesting increased myocardial oxygen demands, e.g. by increased cardiac output.

The blood flow response of the carcass is largely similar in fetuses of 0.75 and 0.9 gestation, in that blood flow falls and recovers during and after asphyxia, respectively. However, at 0.6 gestation carcass blood flow at control is almost twice as high, falls during, and rises above control values after asphyxia. Taking these findings together it appears that in very immature fetuses a state of post-asphyxial hyperperfusion of a number of organs develops, which may reflect a lack of control of vascular resistance. This view is supported by the fact that at this point in gestation, in man and in sheep, as in this study, asphyxia is followed by pronounced hypotension (Jensen, 1991). These observations during arrest of uterine blood flow as well as in part of those from maternal hypoxemia provide evidence that in the very immature fetal sheep at 0.6 gestation circulatory centralization is incomplete and may be ineffective in reducing oxygen delivery to and hence oxygen consumption of peripheral organs (Jensen, Roman, Rudolph, 1991). The fact that the age-dependence of fetal circulatory and metabolic centralization coincides with the maturation of the sympathetic nervous system as well as other neuro-hormonal systems, sheds light on the importance of the sympathetics for intact survival of acute asphyxia.

The relation between O_2 delivery and tissue oxygen consumption

It has been recognized for a long time that hypoxemia and asphyxia cause both a redistribution of blood flow (Campbell *et al.*, 1967; Cohn *et al.*, 1974; Ashwal *et al.*, 1981; Jensen *et al.*, 1987a,b, 1991, Itskovitz *et al.*, 1987) and a reduction in oxygen consumption (Fig. 6a) (Acheson *et al.*, 1957; Parer *et al.*, 1968; Künzel & Moll, 1972; Wilkening & Meschia 1983; Jensen *et al.*, 1987b, 1991). However, only recently a direct relationship between changes in oxygen delivery, i.e. oxygen content x blood flow, to peripheral organs and changes in fetal oxygen consumption has been demonstrated during acute asphyxia (Jensen *et al.*, 1987b) (Fig. 6 b,c). The authors interpreted their findings as an important protective mechanism, which ensures the maintenance of oxidative metabolism in central fetal organs during acute asphyxia, and there is accumulated evidence to support this view (Braems *et al.*, 1990; Braems & Jensen, 1991, Jensen *et al.*, 1991, Asakura *et al.*, 1990).

It is, however, important to notice that this new concept is not at variance with the current understanding of the relation between uterine – and/or umbilical blood flow and fetal oxygen consumption. The relationship between both utero-placental and umbilical blood flow and the oxygen consumption of the fetus is curvilinear (Parer *et al.*, 1968; Künzel & Moll, 1972; Künzel *et al.*, 1977, Wilkening & Meschia, 1983, see Carter, 1989 for review). This implies that fetal oxygen consumption is fairly constant over a wide range of changes in blood flow through the uterine and umbilical circulation. This phenomenon has been observed by many investigators and is largely due to the reciprocal relationship between uterine – and/or umbilical blood flow and oxygen extraction (Clapp, 1978). Thus, depending on the reduction in oxygen delivered caused by the reduction in blood flow, the fetus can increase the amount of oxygen extracted from the blood across both the utero-placental and the umbilical-placental vascular bed, and across the arterio-venous vascular bed of each individual organ. Therefore, the oxygen consumption of the whole conceptus, the fetus, and the individual organs will remain constant over a wide range of changes in oxygen delivery. Oxygen consumption will only decrease when oxygen extraction is maximal and oxygen delivery is reduced further. However, during acute hypoxemia and asphyxia this break point at which tissue oxygen consumption starts to fall can be reached fairly rapidly, though in different organs at different points in time. This is caused by carotid arterial chemoreceptor activation, which results in differential peripheral vasoconstriction mediated largely through sympathetic pathways. Then, both oxygen content and blood flow fall concomitantly, resulting in a dramatic fall in oxygen delivery to and oxygen consumption by peripheral organs. Thus, during asphyxia, circulatory centralization is accompanied by metabolic centralization. This important mechanism, which involves vascular chemoreflexes mediated in part by the sympathetic nervous system has survival value for the fetus (Jensen *et al.*, 1987b).

A number of observations in the fetus and in the adult have contributed to the fact that the possible conclusion that during fetal asphyxia, oxygen delivery might determine oxygen consumption has been precluded for a long time. These include, in the fetus, the constancy of oxygen consumption over a wide range of both uterine and umbilical blood flow changes (see Carter, 1989, for review), in the adult the well-known fact that brain oxygen consumption is constant over a

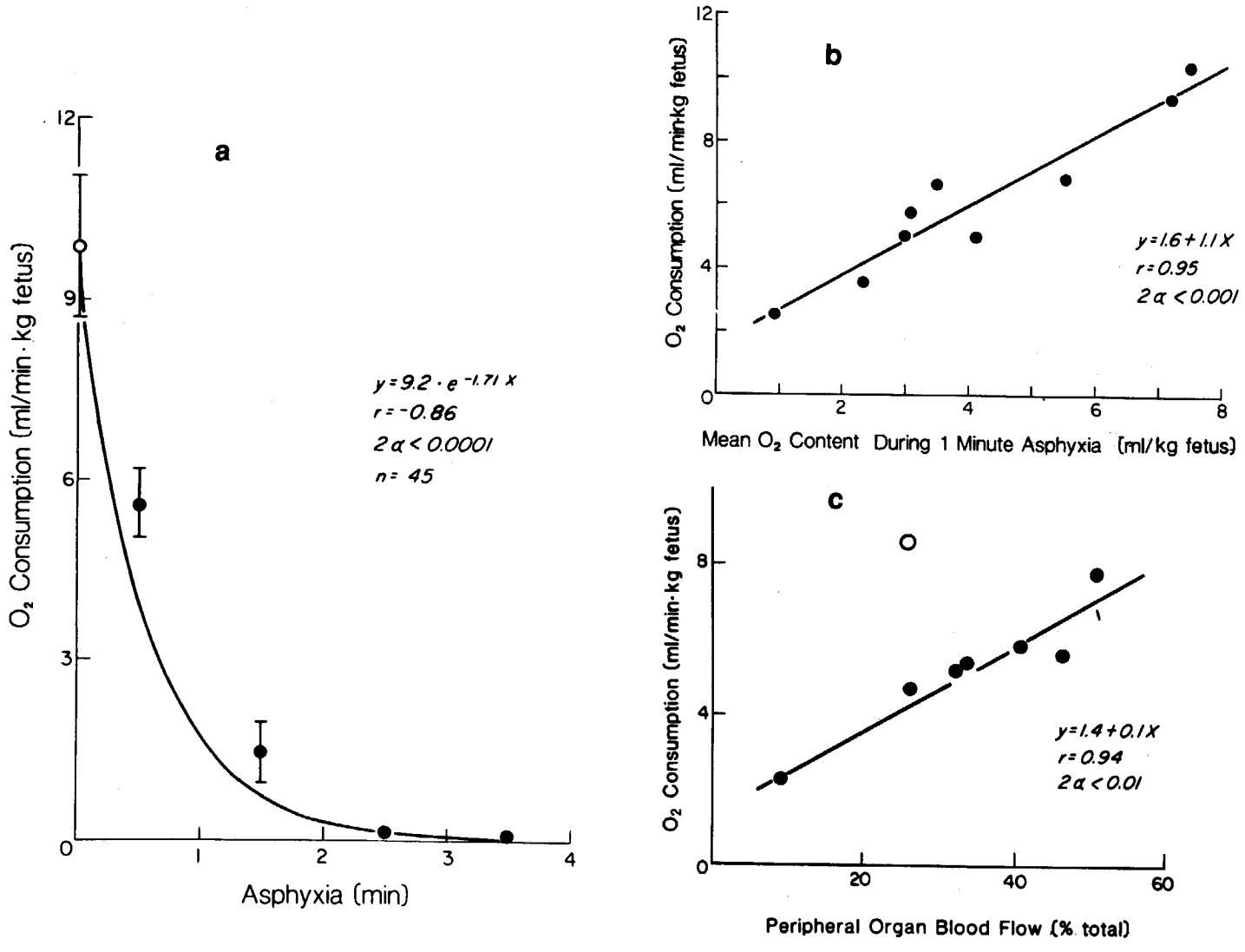

Fig. 6. Changes in fetal and placental oxygen consumption during arrest of uterine blood flow (a). Note, that O_2 consumption falls exponentially during asphyxia. Note also, that O_2 consumption correlates closely with both O_2 content (b) in the descending aortic blood and blood flow to peripheral organs (c). This suggests that in the fetus O_2 delivery is a major determinant of oxygen consumption (Jensen *et al.*, 1987b).

wide range of oxygen partial pressures in the carotid artery, and the fact that mitochondrial oxygen consumption is maintained until oxygen partial pressure falls below a 'critical PO_2' of approximately 1 mmHg (see Siesjö, 1978, for review).

However, at close look, the traditional concept from adult physiology that cellular oxygen consumption is largely unrelated to oxygen availability due to the existence of a very low 'critical PO_2' has been challenged previously. Rosenthal *et al.*, (1976) have reported that cytochrome a_3 is normally more than 20% reduced, and that any decrease and increase in PO_2 will cause reduction or oxidation of cytochrome a_3, raising the question whether there is a 'critical PO_2' at all (Siesjö, 1978). Thus, the matter seems to require some reconsideration, and there are good reasons to believe that the relation between oxygen delivery and oxygen consumption may be different in the fetus, indeed. This is supported by several observations. It has recently been demonstrated for whole cell preparations (Wilson, Owen & Erecinska, 1979), various individual organs, e.g. the carotid body (Acker & Lübbers, 1977), the liver (Bristow, Rudolph, Itskovitz & Barnes, 1983), the kidney (Iwamoto & Rudolph, 1985), organ parts (Jensen, Roman, Rudolph, 1991), and for the whole conceptus (Acheson, Dawes, Mott, 1957; Jensen *et al.*, 1987b) that in the fetus the amount of oxygen available determines the amount of oxygen consumed. Therefore, on the basis of these pieces of conclusive evidence and on the premise that oxygen extraction is maximal, it seems reasonable to conclude that the relation between the availability of oxygen and the consumption of oxygen may be fundamentally different during fetal as compared with adult life, in that oxygen delivery to the tissues determines oxygen consumption by these tissues (Dawes, 1962, Jensen *et al.*, 1987b) (Fig. 6).

Additional support for this important mechanism has been provided *in vivo* by studies on ventilated fetal sheep *in utero* after snaring the umbilical cord (Asakura *et al.*, 1990) and *in vitro* by studies on fetal skeletal muscle cells (Braems & Jensen, 1991),

myocardial cells (Braems, Duβler, Jensen, 1990) and glial cells in monolayer culture (G. Braems, A. Peltzer, A. Jensen, unpublished observations). The *in vitro* studies confirmed the observations *in vivo* showing that in fetal cells oxygen availability is a determinant of cellular oxygen consumption.

The evidence produced so far *in vivo* and *in vitro* suggests strongly that during fetal life on transition from normoxia to hypoxia the fetus is able to reduce oxygen consumption by decreasing oxygen delivery to peripheral organs (Jensen *et al.*, 1987b, Braems & Jensen, 1991). This 'metabolic centralization' helps to maintain oxidative metabolism in central organs by maintaining oxygen delivery to and oxygen consumption of the brain and heart, when oxygen is at short supply (Cohn *et al.*, 1974, Ashwal *et al.*, 1981, Jensen *et al.*, 1987b).

Conversely, on transition from hypoxia to normoxia the increase in oxygen delivery is paralleled by an increase in cellular oxygen consumption and in metabolic drive in most fetal organs. This mechanism, which may be of particular importance on transition from fetal to post-natal life, when oxygen delivery and oxygen consumption rise (Dawes & Mott, 1959) warrants optimal cell function at any given state of oxygenation.

In summary, hypoxia and asphyxia cause centralization of the fetal circulation through chemoreceptor mediated vascular reflexes, which involve, among other vasoactive mechanisms, the activation of the sympathetic nervous system. This circulatory centralization acts in concert with a 'metabolic centralization', which maintains oxygen delivery to, oxygen consumption of and cell function in the brain and heart to ensure intact survival of the fetus (Jensen *et al.*, 1987b, Jensen, 1991).

Cardiovascular mechanisms

The neural and endocrine regulation of the circulation in the fetus and newborn have been reviewed in detail recently (Mott & Walker, 1983). The following account of cardiovascular mechanisms will hence concentrate on the principal responses during oxygen lack.

Near term the common fetal cardiovascular response to acute oxygen lack is bradycardia, an increase in arterial blood pressure and an increase in heart rate variability (Dalton *et al.*, 1977; Walker *et al.*, 1978, 1979; Parer *et al.*, 1980). These changes are in part mediated by peripheral arterial chemoreceptors (Blanco *et al.*, 1984; see Hanson for review, 1988), which co-activate parasympathetic (see Martin, 1985 for review) and sympathetic pathways (Fig. 7) (Cohn *et al.*, 1978; Cohen, Piasecki & Jackson, 1984; Court *et al.*, Jensen *et al.*, 1987a,b,c). This was elegantly illustrated by Blanco *et al.*, (1983) who transected the spinal cord at Th 12 and were then able to show that hypoxemia no longer produced a rise in arterial blood pressure due to ablation of sympathetic efferences, even though the fall in heart rate persisted because the vagi were intact.

Because arterial blood pressure rises there is also an activation of baroreceptors (Blanco et al., 1985), that may result in a further decrease in fetal heart rate. During severe prolonged hypoxemia myocardial suppression and eventually myocardial failure occur (Harris *et al.*, 1982; Itskovitz *et al.*, 1982a). Unlike reflex bradycardia, bradycardia based on myocardial depression cannot be blocked by atropine (Itskovitz *et al.*, 1982a).

There is a correlation between arterial oxygen content before the insult and the delay in the onset of bradycardia. The lower PO_2 in the carotid arterial blood the shorter is the delay in the onset of bradycardia, the greater the decrease in heart rate and the more prolonged the duration of bradycardia (Itskovitz *et al.*, 1982a; Künzel *et al.*, 1983). Conversely, during a reduction in umbilical blood flow the baroreceptor – mediated response precedes that of the carotid chemoreceptors, because arterial blood pressure rises before oxygen content falls.

During prolonged hypoxemia bradycardia tends to normalize. This is associated with an increased sympathetic activity of the neuro- and medullary sympathetic nervous system, which is accompanied by a release of catecholamines from the adrenal medulla and sympathetic nerves (Comline & Silver 1961; Cohen *et al.*, 1982, 1984; Padbury *et al.*, 1981; Jensen *et al.*, 1985, 1987c; Jelinek & Jensen, 1991). The increased release of catecholamines, which in the adrenal medulla amounts to as much as 3–4 milligrams epinephrine and norepinephrine per minutes (Fig. 7) (Cohen *et al.*, 1984), results in a circulatory centralization in favour of the brain, heart and adrenals and at the expense of peripheral organs (see Rudolph, 1984 for review).

If during hypoxemia the sympathetic response is blocked by β-adrenoceptor antagonists the fall of fetal heart rate, cardiac output and umbilical blood flow is more pronounced. Furthermore, increased blood flow to the heart, brain and adrenals cannot be maintained (Cohn *et al.*, 1982; Parer, 1983; Court *et al.*, 1984, Dagbjartsson *et al.*, 1985).

Blockade of alpha-adrenoceptors during hypoxemia causes an increase in fetal heart rate and cardiac output, whereas, arterial blood pressure and total vascular resistance fall (Reuss *et al.*, 1982; Jones & Ritchie, 1983). Then blood flow to the heart, adrenals, gut, spleen, and lungs increase (Reuss *et al.*, 1982). Blockade of alpha- and β-adrenoceptors results in fetal demise during hypoxemia (Parer *et al.*, 1978)

Ablation of peripheral sympathetic neurons by chemical sympathectomy, e.g. by 6-hydroxydopamine, leaves the adrenal medulla intact. Hence, circulating catecholamine concentrations do not change much (Iwamoto *et al.*, 1983; Lewis *et al.*, 1984a; Jensen & Lang, 1988). Changes of cardiac output during and after acute asphyxia are similar in intact as compared with sympathectomized fetuses (Fig. 8) (Jensen & Lang, 1988). However, during fetal hypoxemia and asphyxia

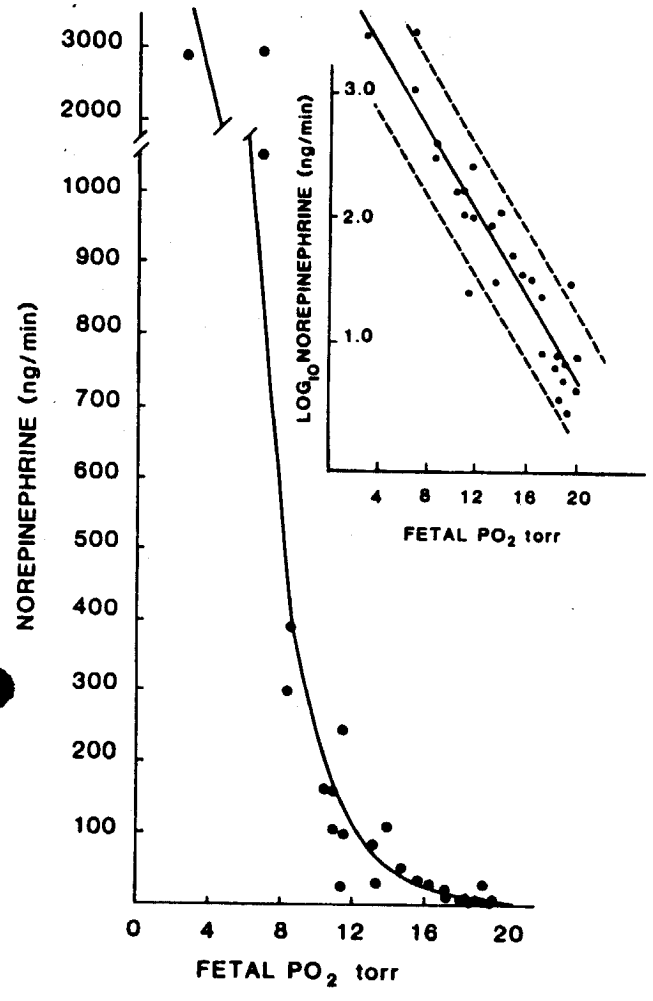

FIG. 4. Relation between fetal arterial PO_2 and adrenal secretory rates of norepinephrine. Pooled data from five animals. Each *point* represents measurement of adrenal secretory rate and equivalent PO_2. n = 28. Exponential equation is $y = 11326e^{-0.39x}$. Linear equation for $\log_{10}$ rectified data is $y = 4.05 - 0.17x$; $r = 0.94$; $P < 0.001$. ---, 95% confidence intervals.

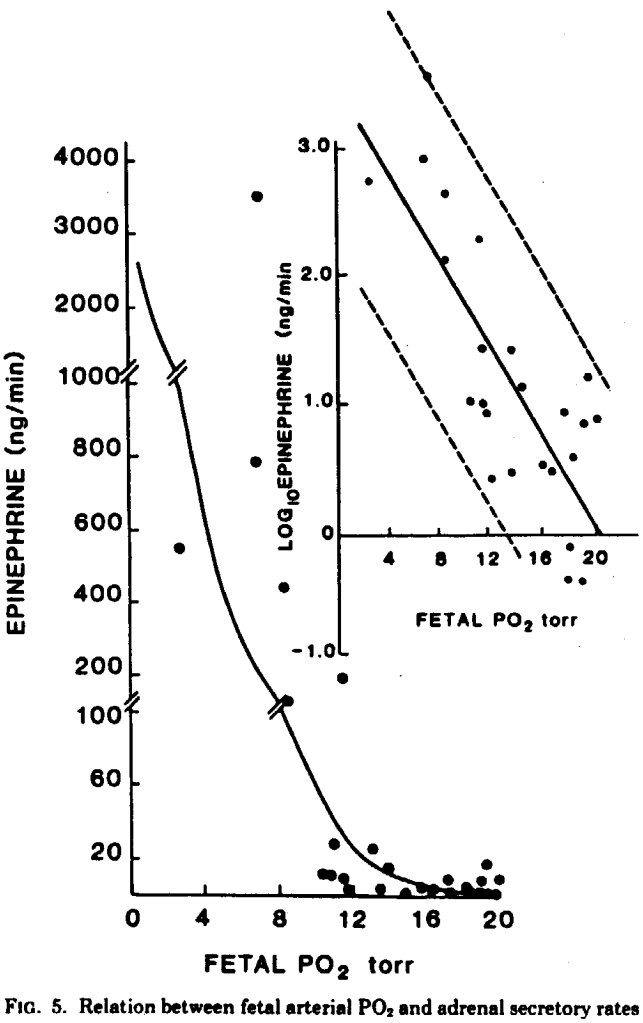

FIG. 5. Relation between fetal arterial PO_2 and adrenal secretory rates of epinephrine. Pooled data from five animals. Each *point* represents measurement of adrenal secretory rate and equivalent PO_2. n = 28. Exponential equation is $y = 3189e^{-0.40x}$. Linear equation for $\log_{10}$ rectified data is $y = 3.44 - 0.17x$; $r = 0.80$, $P < 0.001$. ---, 95% confidence intervals.

Fig. 7. Secretion of catecholamines from the adrenal medulla in chronically prepared fetal sheep (Cohen *et al.*, 1984).

the increase in arterial blood pressure is delayed (Iwamoto *et al.*, 1983; Lewis *et al.*, 1984b; Lewis & Sischo, 1985; Jensen & Lang, 1988). This may be associated with a slow initial rise in plasma catecholamine concentrations (Jones *et al.*, 1988b). In sympathectomized fetuses the redistribution of organ blood flow during hypoxemia and asphyxia is different as compared with intact fetuses (Fig. 8), in that blood flows to the gastrointestinal tract and to the kidneys do not change (Iwamoto *et al.*, 1983; Jensen & Lang, 1988). The effect of chemical sympathectomy on the carcass, skeletal muscle and skin depends on the severity of asphyxia (Iwamoto *et al.*, 1983; Jensen & Lang, 1988). The increase in vascular resistance, which usually occurs during arrest of uterine blood flow, is completely blunted in the gastrointestinal tract and markedly delayed in the carcass (Jensen & Lang, 1988). During maternal hypoxemia the increase in blood flow to the heart, brain and adrenals is not significantly affected in sympathectomized fetuses (Iwamoto *et al.*, 1983). However, during arrest of uterine blood flow the initial increase in blood flow to the brainstem is blunted (Jensen & Lang, 1988). Furthermore, the percent cardiac output directed to the placenta is reduced, while that to the carcass is increased as compared with intact fetuses (Fig. 8). Therefore, in sympathectomized fetuses circulatory centralization is less effective in protecting the fetus against adverse effects of asphyxia (Jensen & Lang, 1988).

But there are also other mechanisms to consider that are involved in the regulation of blood flow during oxygen lack. Fetal hypoxemia is accompanied by an increase in plasma renin activity (Robillard *et al.*, 1981), which converts angiotensin I to angiotensin II, a potent vasoconstrictive hormone (Scroop *et al.*, 1986; Martin *et al.*, 1987b).

Furthermore, there is a rise in vasopressin during hypoxemia (Rurak, 1978). Infusion of vasopressin causes bradycardia and a circulatory centralization (Rurak, 1978, Iwamoto *et al.*, 1979), whereas resting concentrations of vasopressin do not appear to exert major effects on the fetal circulation (Kelly *et al.*, 1983).

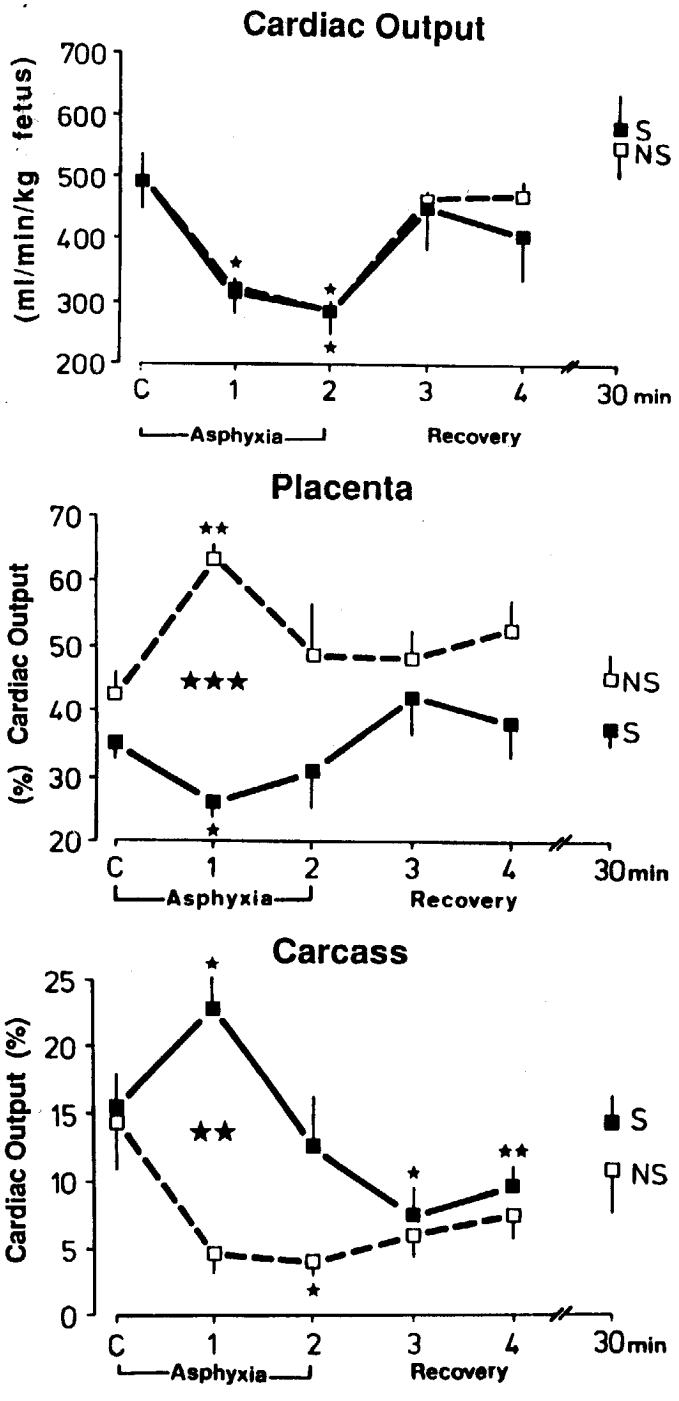

Fig. 8. Cardiac output and its distribution to the placenta and lower carcass of intact (NS) and sympathectomized (S) chronically prepared fetal sheep near term during arrest of uterine blood flow for 2 minutes (Jensen & Lang, 1988).

Also direct effects of vasopressin on the myocardium (Elliot *et al.*, 1985) and on the brain have been described (Courtice *et al.*, 1984).

Acute hypoxia is associated with a reduction in fetal blood volume. In the regulation of these changes the atrial natriurectic factor (ANF) may be involved (Cheung & Brace, 1988). Whether, the rise in ANF concentrations observed during acute hypoxia is a direct or an indirect effect of hypoxia has yet to be determined (Cheung & Brace, 1988).

Circulatory changes during volume loss, e.g. through fetal haemorrhage, are in part governed by the autonomous nervous system (MacDonald, 1980, Brace, 1987). Furthermore, there are a number of hormones released, including arginine vasopressin (Daniel *et al.*, 1978; Drummond *et al.*, 1980; Robillard *et al.*, 1979; Rurak, 1978; Stark *et al.*, 1982, 1984; Rose *et al.*, 1981), renin (Iwamoto &Rudolph, 1981; Robillard *et al.*, 1979, 1982), catecholamines (Cohen *et al.*, 1982; Jones, 1980; Jones *et al.*, 1985; Lewis *et al.*, 1984b, Lewis & Sischo, 1985), ACTH, and cortisol (Rose *et al.*, 1981). Prolonged but quantitatively similar volume losses, e.g. 30% over a period of 2 hours, cause less pronounced hormone changes (Brace & Cheung, 1986).

Furthermore, during hypoxia there is clear evidence for the activation of the pituitary adrenal cortical axis, resulting in increased ACTH and cortisol concentrations (Alexander *et al.*, Boddy *et al.*, 1974b; Jones, 1977; Challis *et al.*, 1986; Bocking *et al.*, 1986b; Towell *et al.*, 1987; Jones *et al.*, 1988b; Challis *et al.*, 1989). Among other responses these two hormones allegedly help to maintain the arterial blood pressure during hypoxemia (Jones *et al.*, 1988b).

Another group of substances related to changes in cardiovascular variables during hypoxemia are β-endorphins (Wardlaw *et al.*, 1981, Stark *et al.*, 1982, Skillman & Clark, 1987). Blocking endogenous opiate receptors by naloxone results in a pronounced fall in heart rate, and a decrease in cardiac output and placental blood flow, while peripheral vascular resistance rises. This suggests that endogenous opoids may modulate the cardiovascular response to hypoxia (La-Gamma *et al.*, 1982, Llanos *et al.*, 1983). Also other peptides, e.g. neuropeptide (NPY) have been reported to cause vasoconstriction, but the actual mechanism has not yet been determined (Emson & Quidt, 1984). Whether endothelial factors are important for changing vascular resistances in the fetus as they are in the adult remains to be established.

In summary, convincing evidence has been produced to show that near term fetal cardiovascular responses to oxygen lack are largely governed by the autonomous nervous systems through parasympathetic and sympathetic pathways. However, there are also a number of other regulatory systems involved into fetal circulatory control and a great variety of vasoactive susbstances exert specific vascular and metabolic effects during hypoxemia and asphyxia through endocrine or paracrine mechanisms. All these regulatory systems ensure – within limits – intact survival of the fetus during asphyxia, but the relative importance of each of these systems for the circulatory and metabolic adaptations of the fetus that are necessary to survive asphyxia may vary during development.

Changes in fetal organs during hypoxemia and asphyxia

Brain

Blood flow to the fetal brain increases during various interventions that result in a fall of arterial oxygen

content. These include maternal hypoxemia (Cohn *et al.*, 1974; Peeters *et al.*, 1979; Ashwal *et al.*, 1981; Carter & Gu, 1988), graded reduction in umbilical blood flow (Itskovitz *et al.*, 1987) and graded reduction in uterine blood flow (Jensen *et al.*, 1991) (Fig. 9). However, during arrest of uterine blood flow, blood flow to the brain does not increase in spite of an increase in arterial blood pressure, suggesting an increase in cerebral vascular resistance (Jensen *et al.*, 1987b). This cerebral reflex vasoconstriction during acute severe asphyxia is accompanied by a steep rise in plasma catecholamine concentrations, suggesting that an activation of the sympathetic nervous system through arterial chemoreceptors is involved (Jensen *et al.*, 1985b; Dawes *et al.*, 1968).

Thus, during asphyxia caused by arrest of uterine blood flow (Jensen *et al.*, 1987b) oxygen delivery to the brain falls, whereas it is maintained during moderate hypoxemia (Jones *et al.*, 1977; Peeters *et al.*, 1979; Jensen *et al.*, 1991; Richardson *et al.*, 1989).

A recent study on the effect of mild chronic hypoxemia (of approximately 17mmHg PO_2 in the fetal ascending aorta) caused by embolization of the umbilical circulation, revealed that here may be threshold arterial oxygen contents, above which cerebral blood flow does not change (Block *et al.*, 1990b). This may be explained in part by an increased oxygen extraction across the cerebral vascular bed, but there are also other mechanisms to consider including a reduced cerebral oxygen consumption.

During hypoxemia the increase in blood flow to the brainstem is greater than that seen in other regions despite the fact that this area has the highest resting blood flow in the fetal brain (Johnson *et al.*, 1979; Ashwal *et al.*, 1981; Jensen *et al.*, 1987b, 1991; Itskovitz *et al.*, 1987, Richardson *et al.*, 1989). This may have survival value for the fetus, because neuronal activity in important autonomous centres in the brainstem is maintained.

Autoregulation of fetal cerebral blood flow is operative in the fetal lamb near term between 30 and 50 mmHg during normoxia (Fig. 10) (Purves & James, 1969; Lou *et al.*, 1979; Tweed *et al.*, 1983; Papile *et al.*, 1985). However, it has been demonstrated that during hypoxemia autoregulation of cerebral blood flow is lost. Then cerebral blood flow varies with arterial blood pressure. But this is not always true. For instance, during acute asphyxia, caused by arrest of uterine blood flow, cerebral vascular resistance increases and hence cerebral blood flow does not increase inspite of a steep increase in arterial blood pressure. Thus, under these very acute conditions, autoregulation of cerebral blood flow is intact, even

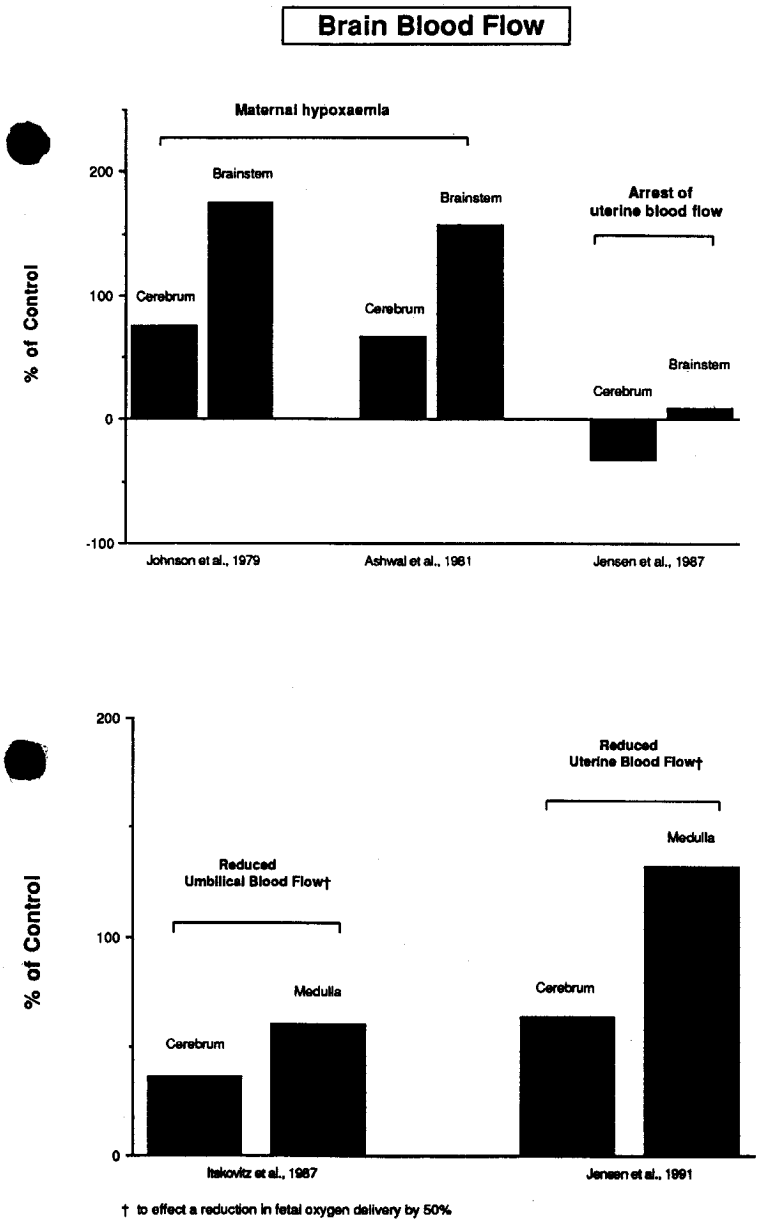

Fig. 9. Blood flow to the cerebrum and to the brain stem (as % of control) during various experimental perturbations in chronically prepared fetal sheep near term. Note, that during arrest of uterine blood flow brain blood flow is redistributed in favour of the brain stem, however, cerebral blood flow fails to increase.

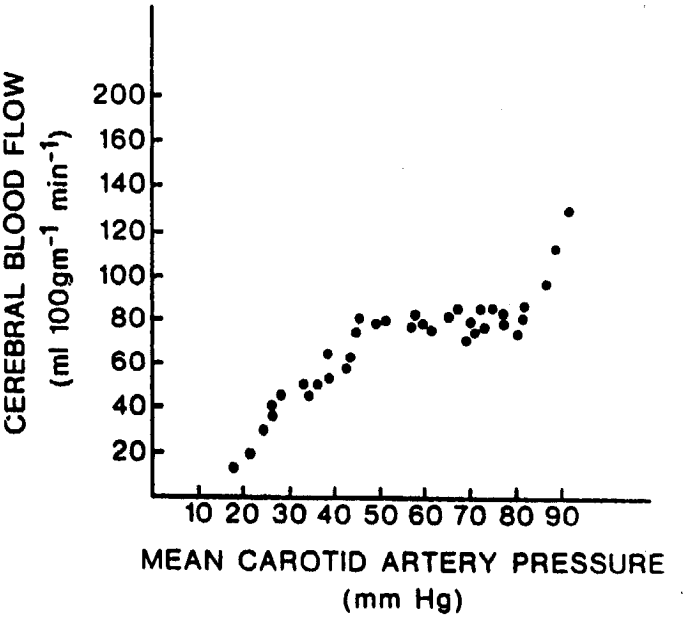

Fig. 10. Autoregulation of brain blood flow in immature chronically prepared fetal sheep (Papile *et al.*, 1985).

though arterial oxygen content is poor (Jensen *et al.*, 1987b). Whether, this is related to the rapidity of the change in carotid arterial oxygen content over time and hence to the intensity of carotid arterial chemoreceptor stimulation, is at present unknown. Interestingly, during repeated occlusion of the umbilical cord, blood flow to the grey matter increased, whereas that to the white matter decreased, a pattern of redistribution that was consistent with brain lesions (Clapp et al., 1988).

A fall in oxygen delivery to the cerebrum can be compensated – within limits – by an increase in cerebral oxygen extraction. If oxygen delivery continues to fall, cerebral oxygen consumption falls (Richardson *et al.*, 1989; Chao *et al.*, 1989). Then, due to increasing cerebral oxygen deficiency, glucose, the main fuel of the brain (Makowski *et al.*, 1972, Richardson *et al.*, 1983), is metabolized anaerobically, lactate concentrations rise, and concentrations of high-energy phosphates fall in the cerebrum (Myers, 1977, 1979; Wagner *et al.*, 1986; Berger *et al.*, 1991). Finally, cerebral metabolism may collapse when synthesis of high-energy phosphates through aerobic or anaerobic glycolysis fails. Then neuronal membranes depolarize and voltage-gated Ca++ flux into the cytoplasm increases. There is also an enhanced release of excitatory neurotransmitters, e.g. glutamate, and hence an increased N-methyl-D-aspirate (NMDH) receptor stimulation. This further opens Ca++ channels and increases the flux of calcium into the neurons (Siesjö & Bengtsson, 1988). Eventually neuronal death occurs.

There are also other adverse effects of asphyxia on the brain, e.g. the generation of oxygen radicals, which destroy multiple unsaturated fatty acids of the cell membranes. These membrane defects lead to a further increase in Ca++ influx, which enhances energy-consuming cellular processes. Then, both membranes and organelles of the neurons will be destroyed by lipases, proteases and endonucleases. Thus, a vicious circle is maintained that eventually results in neuronal death.

Functionally, there are a number of effects elicited by hypoxemia and asphyxia on the brain, e.g. on the electrocortical activity and on fetal breathing. In normoxaemic fetal sheep there are episodic changes in electrocortical activity, characteristic of sleep states postnatally, within 3 weeks of term (Dawes *et al.*, 1972). Then, fetal breathing movements that are almost continuous before 115 days, are confined to episodes of low voltage activity. In this electrocortical state rapid eye movements occur, whereas gross fetal body movement are associated to high voltage electrocortical activity. These obvious functional changes between high and low voltage activity are accompanied by changes in arterial blood presssure, heart rate, blood flow to the brain and to the brainstem and in plasma catecholamine concentrations, suggesting changing sympathetic tone during high and low voltage activity (Jensen *et al.*, 1986, Reid *et al.*, 1990, Walker, dePreu, Horne & Berger, 1990).

The electrocortical activity of the fetus changes during hypoxemia. There is an increase in the relative incidence of episodes of high voltage (Martin *et al.*, 1987a), whereas severe asphyxia is associated with an increased proportion of episodes of low voltage activity. Eventually, fetal electrocortical activity becomes isoelectric (Mann *et al.*, 1970). Interestingly, in chronic hypoxemia, complementary changes of autonomic tone during episodes of low and high voltage electrocortical activity contribute to the slowing of the fetal heart rate. Increased parasympathetic tone and decreased sympathetic tone may enhance cardiac efficiency, when oxygen supply is chronically reduced (Walker *et al.*, 1990).

Fetal breathing movements and REM are reduced during hypoxemia (Dawes, 1973; Boddy *et al.*, 1974a; Nathanielz *et al.*, 1980; Bocking *et al.*, 1986a; Harding *et al.*, 1981; Maloney *et al.*, 1975). This is due to central inhibitions (Dawes *et al.*, 1983; Blanco *et al.*, 1983). During prolonged hypoxemia the incidence of breathing movements returns to normal values within 14 hours (Koos *et al.*, 1988). If carbon dioxide tensions rise, fetal breathing movements are hardly affected (Bissonette *et al.*, 1989).

Transection of the fetal brainstem at the level of the pons eliminates the inhibitory effects of hypoxemia on breathing (Dawes *et al.*, 1983), whereas transection of the spinal medulla T12 -L1 eliminates those on spinal reflexes (Blanco *et al.*, 1983).

Heart

During normoxaemia in the unanesthetized fetal sheep near term, heart rate varies between 160–180 beats and the combined ventricular output varies between 450–600 ml/min/kg fetal body weight. There is only a small rise in cardiac output (10–15%) during tachycardia and only a small increase in stroke volume when end-diastolic filling pressures rise (Gilbert, 1980, 1982; Thornburg & Morton, 1983; Rudolph, 1985). Furthermore, cardiac output is very sensitive to changes in afterload (Gilbert, 1982). These findings suggest that the fetal heart operates at the upper limit of its function curve under physiologic conditions (Rudolph, 1985). This may be related to structural differences between the adult and the fetal heart, in which myofibrillar content is less (Friedman, 1973; Maylie, 1982) and the sarcoplasmatic reticulum and the T-Tubulus-system is poorly developed (Hoerter *et al.*, 1982).

Hypoxemia and asphyxia cause a fall in heart rate and combined ventricular output (Rudolph & Heymann, 1976). Although, arterial blood pressure and hence afterload rise, there is a small increase in stroke volume (Rudolph & Heymann, 1973).

In this situation coronary and myocardial blood flows are increased to meet cardiac oxygen demands by increasing oxygen delivery (Cohn *et al.*, 1974; Peeters *et al.*, 1979; Itskovitz *et al.*, 1987; Jensen *et al.*, 1991). The reduction in preductal aortic oxygen

content by 50% does neither affect cardiac consumption of oxygen nor that of glucose or lactate (Fischer *et al.*, 1982a,b).

Unlike hypoxemia, acidemia reduces cardiac performance (Fischer, 1986; Reller *et al.*, 1986, 1989) a fact that may be related to a depletion of cardiac glycogen stores (Shelley, 1960), which in turn may cause ECG changes (Rosen & Isaksson, 1976; Hökegard et al., 1979).

Liver

The fetal hepatic vascular bed is different from that of the adult, in that the ductus venosus connects the umbilical vein with the abdominal inferior vena cava. There are also branches of the umbilical vein to the left and right liver lobe, the latter communicating with the portal vein (Rudolph, 1983). About 55% of the umbilical venous blood bypasses the liver through the ductus venosus. The remainder is distributed to the liver lobes. The left liver lobe is almost exclusively supplied by umbilical venous blood, whereas the right liver lobe is supplied by both umbilical and portal venous blood. The contribution of hepatic arterial blood is small (3–4%) (see Rudolph 1985, for reviews). During normoxaemia prostaglandins maintain a modest degree of relaxation of the ductus venosus and hepatic microcirculation. However, they are not responsible for the reduction of umbilical venous return between the ductus venosus and the liver during hypoxemia or asphyxia (Paulick, Meyers, Rudolph & Rudolph, 1990).

During maternal hypoxemia to cause a fall in fetal oxygen tension to about 12 mmHg in the carotid artery, umbilical blood flow is largely maintained, whereas fetal blood tends to fall (Cohn *et al.*, 1974). The fraction of umbilical blood distributed to the ductus venosus increases from 55 to 65%, whereas that to the liver falls by a similar amount (Reuss & Rudolph, 1980, Bristow *et al.*, 1983). Due to a reduction of O_2 content in the umbilical venous and portal venous blood, O_2 delivery to the liver falls drastically.

During a reduction in umbilical blood flow, O_2 content does not change, however, hepatic and fetal O_2 delivery fall. This is accompanied by an increased fraction of blood distributed to the ductus venosus at the expense of that to the liver. Within the liver umbilical venous blood flow to the right liver lobe is more reduced than that to the left. Portal venous blood is maintained (Itskovitz *et al.*, 1987; Edelstone *et al.*, 1980).

During reduction in uterine blood flow there is also a redistribution of umbilical venous blood towards the ductus venosus (10%). However, the mechanisms involved are poorly understood. There may be changes in vascular resistance in the ductus venosus related to transmural pressures (Edelstone *et al.*, 1978). But there are also direct hypoxaemic effects and neurohormonal mechanisms to consider (Coceani *et al.*, 1984, Zink & Van Petten, 1980).

During hypoxemia fetal hepatic oxygen consumption falls linearly in relation to the fall in O_2 delivery, but the fall in O_2 consumption is smaller in the left than in the right liver lobe suggesting functional differences (Bristow *et al.*, 1983). During reduction in umbilical blood flow O_2 delivery to the liver decreases, whereas hepatic O_2 consumption is maintained due to an increased O_2 extraction (Rudolph *et al.*, 1989). This apparent contradiction between methods as far as hepatic O_2 consumption is concerned, is largely explained by the amount of oxygen extracted by the liver, which was smaller in the previous than in the latter study.

During maternal hypoxemia or during reduction in uterine blood flow the liver glycogenolysis is enhanced and glucose is released into the inferior vena cava blood. This covers approximately 30–40% of the fetal consumption of glucose when oxygen is at short supply (Bristow *et al.*, 1983; Rudolph *et al.*, 1989). There is no firm evidence for a significant gluconeogenesis in the sheep fetus (Gleason & Rudolph, 1985, 1986). The fall in net lactate uptake of the liver may contribute to the rise in fetal blood lactate concentrations.

Placenta

Umbilical blood flow falls during arrest of uterine blood flow (Jensen, Hohmann & Künzel, 1987b; Jensen, Lang & Künzel, 1987d). However, umbilical and hence placental blood flow is largely maintained during maternal hypoxemia and during graded reduction in uterine blood flow, whereas blood flow to the fetus, particular that to the lower body segment tends to fall (Cohn *et al.*, 1974; Itskovitz *et al.*, 1987; Jensen *et al.*, 1991). At any rate, oxygen delivery from the placenta to the fetus falls. Studies on transplacental diffusion of oxygen in sheep have demonstrated that umbilical and uterine blood form an exchange system that tends to equilibrate the venous concentrations of the two blood streams (Rankin *et al.*, 1971; Wilkening *et al.*, 1982, see Carter, 1989 for review).

The overall efficiency of this exchange system, however, is less than that of an ideal venous equilibration as shown by the observations that the uterine-umbilical venous PO2 difference is consistently positive and ranges among animals between 12 and 20 torr, and that the uterine-umbilical venous PCO_2 - difference is consistently negative and averages approximately -3 torr (Wilkening & Meschia, 1983, Carter, 1989). This limitation may result from several factors, e.g., configuration of maternal and fetal vessels, uneven placental perfusion, low O_2 diffusion capacity, or the high O_2 affinity of fetal blood (Wilkening & Meschia, 1983).

During oxygen lack there is no obvious improvement in the efficiency of the placenta to supply the fetus with oxygen, i.e. to reduce the uterine-umbilical venous O_2-difference. The reduced oxygen delivery to the fetus is compensated initially by an increased O_2 extraction to maintain fetal O_2 consumption. However, below an O_2 delivery of 0.5 mmol/min/kg, fetal O_2 consumption

starts to fall (Parer *et al.*, 1968, Künzel *et al.*, 1977; Wilkening & Meschia, 1983). During reduction in uterine blood flow, net placental consumption of glucose falls and there is evidence for substantial provision of glucose and lactate to the fetus. Fetal production of lactate increases sharply and much of this appears to be consumed by the placenta at a rate sufficient to account entirely for the deficit in net glucose consumption (Gu *et al.*, 1985).

Kidney

During a graded moderate reduction of uterine or umbilical blood flow there are no significant changes in renal blood flow (Itskovitz *et al.*, 1987; Jensen *et al.*, 1991). Maternal hypoxemia causes an increase in renal vascular resistance and a fall in renal blood flow by 20% (Cohn *et al.*, 1974; Weismann & Robillard 1988). However, glomerular filtration rate is maintained suggesting that renal vasoconstriction associated with fetal hypoxemia is likely to occur at the efferent rather than the afferent arteriolar level (Robillard *et al.*, 1981). When renal blood flow falls there is an increase in plasma renin and vasopressin concentrations and an increased reabsorption of water (Robillard al., 1981). Prolonged fetal hypoxemia results in a transient fall in glomerular filtration rate. After 3 hours and during recovery from hypoxemia filtration rate and urine production increase above control values (Wlodeck *et al.*, 1989).

A decrease in renal blood flow during fetal hypoxemia causes a marked reduction in renal oxygen delivery and oxygen extraction increases. Eventually, renal oxygen consumption falls, if hypoxemia persists (Iwamoto & Rudolph, 1985).

During normoxaemia the kidneys metabolize lactate and release glucose, whereas during hypoxemia they metabolize glucose and release lactate (Iwamoto & Rudolph, 1985). Obviously, renal gluconeogenesis prevails during normoxaemia, whereas glycolysis prevails during hypoxia.

Lungs

During fetal life gas exchange occurs in the placenta, and pulmonary blood flow is low supplying only nutritional requirements for lung growth and perhaps serving some metabolic or para-endocrine functions (see Rudolph, 1979 for review; see Heymann, 1984 for review). About 8–10% of the cardiac output are directed to the lungs (Rudolph & Heymann, 1970). The high pulmonary vascular resistance is in part due to the thickness of the vascular smooth muscle (Levin *et al.*, 1976; Hislop & Reid, 1972; Reid, 1979, 1982). Furthermore, physiologically low O_2 partial pressures during fetal life may contribute to an increased pulmonary vascular resistance.

From studies in sheep it has emerged that autonomous control of pulmonary vascular resistance is poor. Bilateral section of cervical or thoracic sympathetic nerves does not significantly change pulmonary vascular resistance (Colebatch *et al.*, 1965). Similarly, bilateral cervical vagotomy had no effect. Also, selective pharmacologic blockade using phentolamine and atropine did not change resting pulmonary vascular tone (Rudolph, Heymann & Lewis, 1977). Interestingly, a combination of alpha- and beta-adrenergic with parasympathetic blockade could prevent pulmonary vasoconstriction (Lewis *et al.*, 1976), suggesting that pulmonary vascular responses to hypoxia are not mediated directly by these autonomic pathways (Heymann, 1984). On the other hand, electrical (Colebatch *et al.*, 1965), and hormone receptor stimulation (Cassin *et al.*, 1964a,b; Barett *et al.*, 1972; Smith *et al.*, 1964) could alter pulmonary vascular resistance. Whether these mechanisms are invoked during fetal hypoxemia is not clear (Heymann, 1984).

Prostaglandins have been reported to be involved into the regulation of pulmonary blood flow, however, the specific effects are variable (Tyler *et al.*, 1977; Lefffler & Hessler, 1979; Cassin, 1980; Cassin *et al.*, 1981). At present it appears that prostaglandins have at least a modulatory effect on pulmonary vasoconstriction during hypoxemia, which is blunted by indomethacin, a potent inhibitor of cyclooxygenase dependent products of prostaglandin metabolism (Leffler *et al.*, 1978; Cassin, 1982). Recently, further evidence for a major role of leucotriens, lipooxygenase dependent derivatives of arachidonic acid metabolism, in regulating pulmonary blood flow has been produced. Maternal hypoxemia, graded reduction of umbilical and uterine blood flow increase pulmonary vascular resistance and decrease pulmonary blood flow (Cohn *et al.*, 1974; Lewis *et al.*, 1976; Peeters *et al.*, 1979; Itskovitz *et al.*, 1987; Jensen *et al.*, 1991). In immature and mature human newborns there is evidence that reduced pulmonary blood flow during asphyxia might be related to both patent ductus arteriosus and respiratory distress syndrome.

Adrenals

Adrenal blood flow increases during maternal hypoxemia, graded reduction in uterine and/or umbilical blood flow (Cohn *et al.*, 1974; Itskovitz *et al.*, 1987; Jensen *et al.*, 1991), suggesting that this organ is important when oxygen is at short supply. Therefore, the adrenals are considered to be 'central' organs along with the brain and the heart. During normoxaemia adrenal medullary blood flow (511 ± 155 ml/min/100g) is twice as high as adrenal cortical blood flow (248 ± 71 ml/min/100g). During isocapnic hypoxemia the increase in blood flow (+145%) is similar in the two adrenal areas (Jensen *et al.*, 1985). These changes in blood flow may be related to adrenal function, in that catecholamines, e.g. norepinephrine and epinephrine, are released during hypoxemia in large quantities from the adrenal medulla (Comline & Silver, 1961; Jelinek & Jensen, 1991). There is also a significant release of cortisol (Jones, 1977, Jones *et al.*, 1977), which is related to an increased release of ACTH from

the pituitary (Jones *et al.*, 1988b), and of aldosterone (Robillard *et al.*, 1984).

During severe asphyxia, caused by arrest of uterine blood flow, the release of medullary and cortical hormones is different in that concentrations of norepinephrine, epinephrine, and aldosterone increase and those of cortisol, dehydroepiandrosterone decrease. Furthermore, there appears to be a redistribution of adrenal corticosteroid biosynthesis during asphyxia, in favour of the cortisol pathway and at the expense of the androgen pathway (Jensen *et al.*, 1988).

Intestines

Blood flow to the intestinal tract is maintained during maternal hypoxemia and during graded reduction in uterine and umbilical blood flow (Cohn *et al.*, 1974; Edelstone & Holzman, 1984; Itskovitz *et al.*, 1987; Jensen *et al.*, 1991), and intestinal oxygen consumption does not change, because oxygen extraction rises (Edelstone & Holzman, 1982). Only severe reduction in fetal arterial oxygen content results in a marked fall in intestinal blood flow to very low values (Jensen *et al.*, 1987b; Yaffe *et al.*, 1987). Then, in spite of an increased oxygen extraction, intestinal oxygen consumption falls and a mesentery acidosis develops (Edelstone & Holzman, 1982, 1984). In human newborns this might be related to necrotizing enterocolitis.

Spleen

Splenic blood flow is reduced during maternal hypoxemia, graded reduction in uterine blood flow (n.s), and severe asphyxia caused by arrest of uterine blood flow. During the latter insult, splenic blood flow is virtually arrested (Jensen *et al.*, 1987b; Jensen & Lang, 1988). This may be related to the fact that the spleen is almost exclusively innervated by the sympathetics (Fillenz, 1966).

Carcass

The fetal carcass largely consists of skin, muscle, bones and connective tissues. Blood flow to the carcass falls during more severe maternal hypoxemia or a reduction in uterine blood flow (Cohn *et al.*, 1974; Jensen *et al.*, 1991). It rises, however, during graded reduction in umbilical blood flow (Itskovitz *et al.*, 1987). Interestingly, oxygen consumption of the carcass decreases twice as much during uterine blood flow reduction (Jensen *et al.*, 1991) than during umbilical blood flow reduction (Itskovitz *et al.*, 1987), even though in both studies total fetal oxygen delivery is reduced by similar amounts, i.e. by 50%. This suggests that the delivery of oxygen to the carcass, which is considerably lower in the former study, determines the consumption of oxygen in the carcass (Fig. 11). This view is supported by findings in the studies in which uterine blood flow was arrested (Jensen *et al.*, 1987b) (Fig. 6). These studies provided first evidence that the amount of oxygen delivered to peripheral organs determines the amount of oxygen consumed by these organs (Jensen

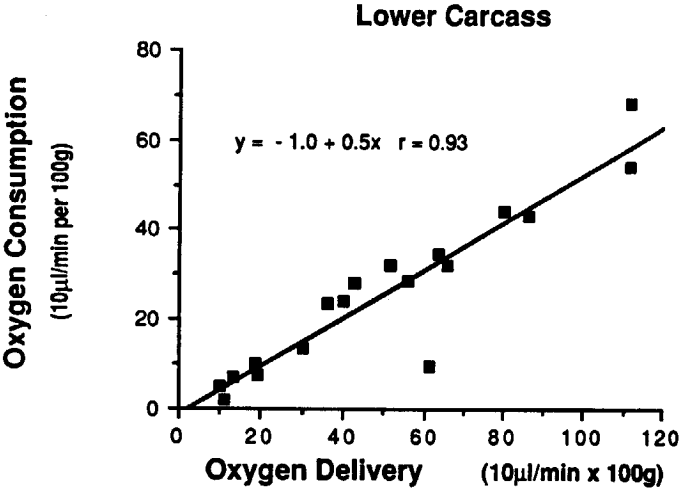

Fig. 11. Close correlation between O_2 delivery and O_2 consumption in the lower carcass of chronically prepared fetal sheep near term during graded reduction in uterine blood flow. Note, that O_2 delivery determines O_2 consumption when oxygen is at short supply (Jensen *et al.*, 1991).

et al., 1987b). This important mechanism enables the fetus to conserve oxygen in peripheral organs, e.g. the carcass, to maintain oxidative metabolism in central organs when oxygen is at short supply.

Body skin and scalp

For a long time, reduced blood flow to the skin of the neonate has been recognized as an index of asphyxia and hence of circulatory redistribution (Stein, 1783; Schulze, 1871; Apgar, 1953). However, only recently blood flow to the skin of the fetus has been studied systematically, to establish whether changes in cutaneous blood flow reflect a centralization of the fetal circulation (Fig. 2) (Jensen & Künzel, 1980; Jensen *et al.*, 1985, 1987a,b,c,d).

In normoxaemic fetal sheep near term blood flow to the skin of the hips and shoulders is about 22-26 ml/min/100g and that to the scalp is significantly higher and ranges between 29-34 ml/min/100g (Jensen *et al.*, 1986, Jensen, 1989). During isocapnic hypoxemia with a carotid arterial PO_2 of 12 mm Hg, blood flow to the skin and scalp fall by 18% and 23%, resp., as do blood flows to most of the peripheral organs, including the lungs (Jensen, 1989).

Graded reduction in uterine blood flow reduces blood flow to the skin and scalp by about 50-60% (Jensen *et al.*, 1991), whereas arrest of uterine blood flow reduces blood flow to the skin by 95% and that to the scalp by 85% (Jensen *et al.*, 1987b). At control and during acute asphyxia blood flows to the two cutaneous areas correlate linearly, however, throughout acute asphyxia blood flow to the scalp is 5 to 10 times higher than that to the body skin, indicating a different responsiveness of the skin vasculature in certain area (Jensen *et al.*, 1985, Jensen *et al.*, 1987a). The fact that during acute asphyxia the time course of the fall in blood flow to peripheral organs is largely similar to that in the skin and scalp, suggests that decreased cutaneous blood flow reflects redistribution of the fetal circulation (Jensen *et al.*, 1985, 1987a,b,c,d). This is related to the fact

that asphyxia increase sympathetic nervous activity through arterial chemoreceptor mechanisms and hence causes an almost generalized peripheral vasoconstriction (Dawes *et al.*, 1968).

Skin blood flow is quite sensitive as an index of circulatory centralization, because blood flow to the skin decreases more than that to any other peripheral organ. Furthermore, skin blood flow depends largely on sympathetic activity, which is known to increase rapidly during asphyxia through chemoreceptor-mediated mechanisms (Hanson, 1988).

In summary, during hypoxemia and asphyxia there is a circulatory centralization in favour of the brain, heart, and adrenals and at the expense of almost all peripheral organs, particularly of the lungs, carcass, skin and scalp. This response is qualitatively similar but quantitatively different under various experimental conditions. However, at the nadir of severe acute asphyxia the circulatory centralization cannot be maintained. Then there is circulatory decentralization, and the fetus will experience severe brain damage if not expire unless immediate resuscitation is provided. Future work in this field will have to concentrate on the important questions, what factors determine this collapse of circulatory compensating mechanisms in the fetus, how does it relate to neuronal damage, and how can the fetal brain be pharmacologically protected against the adverse effects of asphyxia. As far as neuroprotection is concerned, it will be of utmost importance to exclude any interference of neuroprotective drugs with life-saving cardiovascular mechanisms, e.g. circulatory and metabolic centralization, that are naturally operative and have proven to be so effective in protecting both life and central nervous systems of asphyxiated fetuses and newborns.

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