The effects of hypoxaemia in fetal sheep

J. S. ROBINSON, C. T. JONES, AND G. D. THORBURN

From the Nuffield Institute for Medical Research, Headley Way, Headington, and the Nuffield Department for Obstetrics and Gynaecology, Oxford

Fetal hypoxaemia may result from altered maternal PaO_2 or a reduction in maternal placental or umbilical blood flow. It is also possible that reduction of gas exchange across the placenta could limit the oxygen supply to the fetus. In this review we will be concerned with the effects of hypoxaemia in fetal sheep during the latter half of pregnancy.

At present it is not easy to reduce maternal placental blood flow experimentally in a controlled manner, while an acute restriction of umbilical blood flow results in asphyxia (Towell and Salvador, 1974). Fetal hypoxaemia can be induced reproducibly by lowering maternal inspired oxygen concentrations and hence PaO_2 . During such experiments, the fetal blood gas tensions take several minutes to equilibrate while the cardiovascular and plasma changes require up to 60 min to reach a relatively steady state (Boddy *et al*, 1974a; Cohn *et al*, 1974; Jones and Robinson, 1975; Rurak, 1976a and b; Jones, 1977). Although the acute episodes of hypoxaemia known to occur spontaneously last only a few minutes (Jones and Ritchie, 1976; Patrick *et al*, 1976), studying changes over a 60-min period provides more detailed information.

A different approach has been used to produce long-term hypoxaemia in the fetus so as to minimize the effects on the mother. This has been either to reduce placental mass surgically (Alexander, 1964), to embolize the maternal placenta with microspheres (Creasy *et al*, 1972), or to reduce umbilical blood flow by umbilical artery ligation (Emmanouilides *et al*, 1968).

It is important when investigating fetal hypoxaemia to avoid the effects of anaesthesia and surgery. Such acute experiments are associated with much higher hormone (at least 10 fold higher for ACTH, catecholamines and vasopressin) and metabolite concentrations than in chronically catheterized fetal preparations. For instance, the plasma catecholamine concentration in the exteriorized fetal sheep is higher than that normally seen during hypoxaemia in fetal sheep *in utero* (Jones and Robinson, 1975; Jones and Rurak, 1976a) and hypoxaemia causes a tachycardia

in the exteriorized fetus compared with an initial bradycardia *in utero*. We will therefore concentrate on the cardiovascular, metabolic and endocrine changes observed with both short-term and chronic hypoxaemia in the conscious unrestrained sheep with implanted catheters.

Short-term hypoxaemia

CARDIOVASCULAR CHANGES

During experiments in which ewes were given 9 per

Fig 1 The effects of hypoxaemia (a) and hypoxaemia plus propranolol infusion (b) on the heart rate of fetal sheep of 125 days; (■) hypoxaemia induced by causing ewes to breathe 9 per cent O_2 plus 3 per cent CO_2 ; (▨) propranolol infused at 44 $\mu\text{g}/\text{min}$ into a fetal jugular vein.

cent oxygen and 3 per cent carbon dioxide in nitrogen to breathe for one hour, fetal carotid arterial PaO_2 fell from about 25 to 16 mm Hg while PaCO_2 remained steady. In most instances a small (about 0.06) but significant fall of pH occurred (Boddy *et al*, 1974a). The cardiovascular changes observed with this degree of hypoxaemia varied with gestational age. The heart rate in young fetuses (< 102 days, term ~ 145 days) increased by about 50 beats min^{-1} but there was no significant change in arterial pressure. The initial response in older fetuses (> 119 days), however, was a bradycardia, the heart rate falling by about 30 beats min^{-1} , and this was accompanied by a 5–10 mm Hg increase in arterial pressure (Boddy *et al*, 1974a; Cohn *et al*, 1974; Jones and Robinson, 1975; Rurak, 1976a and b) (fig 1a). The rise of arterial pressure is mainly due to activation of aortic body chemoreceptors (Dawes *et al*, 1969) and causes a bradycardia as a result of stimulation of the baroreceptors (Shinebourne *et al*, 1972). Bilateral cervical vagotomy abolishes the rise in arterial pressure with hypoxaemia and the fetal heart rate increases as in the younger fetuses (Boddy *et al*, 1974a; Rurak, 1976b).

Although Boddy *et al* (1974a) noted that the fetal heart rate gradually increased during hypoxaemia, Jones and Robinson (1975) found that the bradycardia persisted in some fetuses. They measured plasma noradrenaline and adrenaline concentrations and reported that both increased during hypoxaemia. The bradycardia persisted in those fetuses in which the catecholamine concentration was < 3 ng/ml whereas the heart rate increased when it was > 8 ng/ml suggesting that high plasma catecholamine concentrations overcame vagal inhibition of the heart. Ritchie (1975) found that infusion of adrenaline (1.3 $\mu\text{g}/\text{min}$) in fetal sheep increased arterial pressure and the heart rate fell, then rose (fig 2).

This rise in heart rate was prevented by the β blocker, propranolol. When propranolol was infused during hypoxaemia, at a rate known to block the effects of circulating catecholamines on the heart, increased arterial pressure and persistent bradycardia occurred which suggests persistence of vagal activity (Jones and Ritchie, unpublished) (fig 1b). This indicates some of the ways in which the fetal heart rate may be under adrenergic control and it must be borne in mind that as the catecholamine stores of the fetal heart are low (Friedman, 1972) its sensitivity to exogenous catecholamines will be high (Friedman *et al*, 1968).

The increase in arterial pressure has been attributed to aortic body activity but may also result from the release of antidiuretic hormone (ADH) during hypoxaemia. Rurak (1976a and b) demonstrated a rise of ADH with hypoxaemia which cor-

Fig 2 The changes in heart rate during the infusion of adrenaline into fetal sheep of 127 to 129 days; (a) adrenaline was infused into the fetal jugular vein at 1.3 $\mu\text{g}/\text{min}$; (b) propranolol was infused at 44 $\mu\text{g}/\text{min}$ together with adrenaline; (c) phentolamine was infused at (100 $\mu\text{g}/\text{min}$) together with adrenaline; ■ shows the period of adrenaline infusion.

related with the change in arterial pressure. He also showed that fetal infusion of ADH to achieve similar plasma concentrations increased arterial pressure. Vagotomy blunted but did not abolish the ADH release during hypoxaemia.

The acute experiments of Dawes and his colleagues (see Dawes, 1968) demonstrated redistribution of cardiac output during hypoxaemia with reduced blood flow to the lungs and hind limbs. This has been re-examined in the chronic fetal sheep preparation using radioactively labelled microspheres by Cohn *et al* (1974). They separated the fetuses into two groups depending on the presence or absence of acidemia during hypoxaemia. During hypoxaemia the proportion of cardiac output distributed to the placenta, heart, brain and adrenals increased, whereas the cardiac output and the flow to the gut, spleen, kidneys and carcass decreased (table I). The greatest changes were observed in the group which developed acidemia.

	Control	Hypoxaemia	Control	Hypoxaemia + Acidaemia
Cardiac output (ml min ⁻¹ kg ⁻¹)	464	442	497	381*
Umbilical blood flow (ml min ⁻¹ kg ⁻¹)	191	213	195	205
Percentage distribution of cardiac output to placenta	41.1	47.8†	41.6	56.6*
Organ blood flow (ml min ⁻¹ 100g ⁻¹)				
Gut	67	53	96	41†
Spleen	240	80†	352	50*
Kidneys	175	136*	162	81†
Carcass	20	14	20	6*
Lungs	60	27	57	32†
Heart	179	449*	185	482†
Brain	96	168*	120	185*
Adrenals	271	828*	302	855†

Table I Cardiac output and organ blood flow during hypoxaemia (Cohn et al, 1974)

*P < 0.01, †P < 0.05.

Episodes of spontaneous hypoxaemia have been observed in fetal sheep. These are usually characterized by a rise in arterial pressure of up to 50 per cent accompanied by a rapid fall in heart rate by about 50 per cent which may last several minutes. They are associated with compression of the umbilical cord (by entanglement with limbs or vascular catheters) or with uterine activity (Jones and Ritchie, 1976; Patrick et al, 1976). During the bradycardia there is a decrease of PaO₂ accompanied by an increase in PaCO₂ and a fall in pH. These episodes may occur two or three times per hour and can result in abrupt fetal death (fig 3). The metabolic and endocrine changes occurring during these episodes are described below.

ENDOCRINE CHANGES

During fetal hypoxaemia the plasma concentrations of growth hormone, luteinizing hormone, prolactin and oxytocin show no consistent changes (Alexander, et al, 1973b; C. McMillen, unpublished observations). In contrast plasma ADH concentrations increase substantially during hypoxaemia (Alexander et al, 1973b; Rurak, 1976a and b) and are associated with an inhibition of diuresis and an increase in urine osmolarity (D. Walker, unpublished observations). Bilateral cervical vagotomy can block the rise in plasma ADH concentration (Jones and Rurak, 1976b) but this effect is not always seen (Rurak, 1976a and b).

Fig 3 Two episodes of bradycardia and elevated arterial pressure in a fetal sheep at 139 and 140 days. The final episode resulting in abrupt fetal death illustrates the initial rise then gradual fall in arterial pressure observed with acute asphyxia.

The concentration of adrenocorticotrophin (ACTH) in the fetal circulation increases considerably in response to hypoxaemia (Alexander et al, 1973b; Boddy et al, 1974b; Jones et al, 1977) which is unlikely to be the result of activation of the aortic body chemoreceptor as it is not influenced by vagotomy. It is apparent that the hypoxic stimulus does not act at the hypothalamic or pituitary level since mid-brain section blocks the ACTH rise during hypoxaemia (Robinson, Rees, Kendall and Thorburn, unpublished observations). The physiological significance of the rises of ACTH during hypoxaemia is not clear since the corticosteroid output of the fetal sheep adrenal is relatively unresponsive to ACTH until five to 10 days before birth (Bassett and Thorburn, 1973; Madiill and Bassett, 1973; Jones et al, 1977). Indeed it is only late in gestation that there is a large corticosteroid response to hypoxaemia (fig 4). Daily periods of hypoxaemia for 60 min, which consistently elevate the concentration of ACTH in fetal plasma, induce the maturation of the corticosteroid response of the fetal adrenal (Jones et al, 1977).

In contrast, the adrenal medullary hormones, adrenaline and noradrenaline, exhibit increases in both adrenal output and plasma concentration (fig 4) in response to hypoxaemia (Comline and Silver, 1961; Jones and Robinson, 1975). During the last 20-30 days of intrauterine life there are no changes in the response to moderate hypoxaemia although there is a large increase in the adrenal response to asphyxia and severe hypoxia. The source of the circulating catecholamines is not entirely clear. Some (particularly dopamine) may originate from paraganglia that are also responsive to hypoxia (Brundin, 1966).

The plasma concentration of pancreatic glucagon increases up to tenfold during hypoxaemia (J. R. Girard and H. J. Shelley, personal communication) while plasma insulin does not change or falls despite a rise in plasma glucose (figs 4 and 5). The plasma insulin concentration, at least, may be under

Fig 4 The changes in the concentration of hormones in the plasma of fetal sheep during hypoxaemia. A 118-125 days, B 140-146 days. (●), ACTH (pg/ml); (○), corticosteroid (ng/ml); (■), insulin (μ Units/ml); (▲), adrenaline (ng/ml); (▬) hypoxaemia was induced by causing pregnant sheep to breathe 9 per cent O₂ + 3 per cent CO₂ in N₂.

Fig 5 The changes in the concentration of plasma metabolites during hypoxaemia in fetal sheep, A 118-122 days, B 140-146 days. (●), glucose; (○), free fatty acid; (▲), lactate (▬) hypoxaemia was induced by causing pregnant sheep to breathe 9 per cent O₂ + 3 per cent CO₂ in N₂.

adrenergic control (particularly that of circulating catecholamines) since α -adrenergic blockade with phentolamine during hypoxaemia is associated with an increase in fetal plasma insulin concentration.

The changes in plasma ACTH and cortisol concentrations observed during a 60-min period of experimental hypoxaemia have also been seen during short periods of spontaneous hypoxaemia *in utero* (Jones and Ritchie, 1976).

METABOLIC RESPONSES

During the course of fetal development tissue glycogen stores change dramatically (Dawes and Shelley, 1968). The concentration in the liver and

muscle increases in the last third of gestation. In contrast, the glycogen concentration in the heart and lung is initially high and then decreases. Thus it might be expected that the plasma lactate and glucose responses of the fetal sheep to hypoxia change with gestational age (Alexander *et al*, 1972; Shelley, 1973; Jones, 1977). Of the organs mentioned above, only the liver is capable of mobilizing glycogen to glucose (Scrutton and Utter, 1968) and the increase in hepatic glycogen in the fetal sheep is associated with a rise of plasma glucose in response to hypoxaemia (Jones, 1977). Before 120 days hypoxaemia causes little change in plasma glucose concentration while between 120 days and term the

response becomes progressively larger (fig 5). It is likely that some of the glucose increase is the result of glycogen mobilization and similar rises in response to adrenaline or isoprenaline infusion support this view as does stimulation of glycogenolysis in the perfused fetal liver by adrenaline (Bassett and Jones, 1976). The absence of a change or a fall in plasma insulin concentration is clearly also important since the α -blocker, phentolamine, which prevents adrenergic inhibition of insulin secretion (Woods and Porte, 1974), blocked the hypoxia-induced rise in glucose (Bassett and Jones, 1976).

Normally hypoxaemia causes four to eight-fold increases in plasma lactate concentration (fig 5) and the high lactate concentration persists for several hours after hypoxia (Britton *et al*, 1967b; Alexander *et al*, 1972; Shelley, 1973; Jones, 1977). Despite the large changes in tissue glycogen concentration, these responses did not change significantly over the latter third of pregnancy (Jones, 1977). Apart from the large glycogen stores, which are depleted during hypoxaemia (Shelley, 1973), the relative impermeability of the sheep placenta to lactate (Britton *et al*, 1967a) and the probable inability of the fetal tissue to increase their lactate consumption (Jones, 1977) contribute to the persistent high plasma lactate concentration. The placenta is also an important source of lactate (Burd *et al*, 1975; Jones and Rurak, 1976a) and placental lactate output increases during hypoxia (C. T. Jones and D. Walker, unpublished observations).

The fetal sheep has little stored fat (Body and Shorland, 1964; Body *et al*, 1966) and this is reflected in the very low plasma concentration of free fatty acid (Van Duyn *et al*, 1960). There is, however, a rise in the plasma concentration during the latter third of pregnancy but even close to term it is still a tenth of the maternal concentration (Jones, 1977). During hypoxaemia there is little change in the plasma concentration of free fatty acid in the fetus until after 130 days and substantial increases are not seen until several days before birth (fig 5). The increase in free fatty acid concentrations in plasma during hypoxaemia correlate with the rise in plasma catecholamines (Jones, 1977) and may be related to the development of the response of the adrenal medulla to hypoxaemia (Comline and Silver, 1961). Plasma ketone body concentrations parallel those of the free fatty acids both at rest and during hypoxaemia (Jones, 1977). Since the liver of the fetal sheep metabolizes fatty acids to ketone bodies several days before birth (Alexander *et al*, 1973a), a close correlation between the two is not surprising.

The metabolite changes seen during experimental hypoxaemia have been observed during short periods of spontaneous hypoxaemia (Jones and Ritchie, 1976).

Long-term or chronic hypoxaemia

CARDIOVASCULAR CHANGES

Chronic hypoxaemia in fetal sheep has been produced experimentally by interference with the placental vasculature. Emmanouilides *et al* (1968) ligated one umbilical artery and demonstrated hypoxaemia in association with reduced fetal weight at delivery but did not report any cardiovascular changes.

The sheep uterus contains folds of endometrium called caruncles, some of which form the maternal cotyledons in pregnancy. Removal of caruncles results in a reduction of placental size in a subsequent pregnancy, and Alexander (1964) demonstrated that this is associated with an increased incidence of intrauterine deaths, premature delivery and reduced birthweight. Using this technique Robinson *et al* (1976) observed fetal growth retardation in three of six pregnancies. The growth-retarded fetuses were chronically hypoxaemic (PaO₂ down by 37 per cent) while the normal-sized fetuses were hypoxaemic late in gestation. Recordings of fetal heart rate and arterial pressure have been made in five fetuses (three small and two normal sized). In all fetuses the resting heart rate and blood pressure were similar to controls. However, in two small and one normal-sized fetus spontaneous periods of bradycardia (fig 6) similar to those described earlier but with no simple physical explanation were observed.

Long-term reduction of fetal PaO₂ (down by 15 per cent) with raised haematocrit and no acidaemia has been produced by embolization of the maternal side of the placenta by daily injections of 15 μ microspheres into the uterine circulation (Creasy *et al*, 1972, 1973). Embolization resulted in significantly reduced placental and fetal weight with changes in organ weights similar to that described in the growth-retarded human fetus (Gruenwald, 1963;

Fig 6 Spontaneous fetal bradycardia and increased arterial pressure in a normal-sized fetus. These episodes occurred with gradually increasing frequency from 137 days until delivery. Before pregnancy the number of placental attachment sites was reduced by removal of endometrial caruncles.

Naeye, 1965). At about 139 days fetal cardiac output and its distribution were measured using radioactively labelled microspheres and compared with controls. Fetal cardiac output was reduced by approximately one third in the embolized group. The proportion of cardiac output distributed to the brain, heart, kidney and gut was increased while that to the placenta and lung was reduced (table II).

	Control	Embolized
Cardiac output (ml min ⁻¹)	1807	1171*
Percentage cardiac output to		
Brain	3.4	6.8*
Heart	2.3	4.5*
Gut	6.6	10.8*
Kidney	3.1	5.0*
Lung	5.4	1.7*
Placenta	41.9	29.1*

Table II Distribution of fetal cardiac output with embolization of the uterine circulation (Creasy et al, 1973)

*P < 0.05.

ENDOCRINE CHANGES

Relatively little information exists on the effects of long-term hypoxaemia on hormone concentrations in the fetus. During hypoxaemia induced by a surgical reduction of placental mass fetal plasma ACTH concentration remains low for most of the period of observation and plasma insulin is about half its normal concentration.

METABOLIC RESPONSES

Hypoxaemia for longer than 60 min causes a fall in hepatic glycogen (Shelley, 1973) in association with maintenance of a high fetal plasma glucose. Clearly this cannot persist and in long-term hypoxaemia there is a low plasma glucose and high plasma lactate (Shelley, 1973). In chronic hypoxaemia caused by a reduction of placental mass a persistently low plasma glucose concentration is also seen but with a low plasma lactate concentration. Thus a low fetal blood glucose concentration is likely to be a feature of chronic hypoxaemia while the plasma lactate concentration will possibly be dependent on the origin of the hypoxaemia.

Conclusion

The changes occurring in the fetus during short-term hypoxaemia are probably essential for the function of vital organs at the expense of others. The redistribution of cardiac output increases flow to the brain and heart while reducing that to other tissues such as muscles and lungs. At the same time there is mobilization of hepatic glycogen and a reduction of glucose

uptake by the insulin-sensitive tissues improving the supply of glucose to the brain. This is an important factor in survival during asphyxia (Dawes et al, 1966; Mann, 1970).

Accounting for the changes observed during chronic hypoxaemia is more difficult. Redistribution of cardiac output similar to that seen with short-term hypoxaemia occurs. The reduced flow to some organs may be partly responsible for their reduced growth. But the low plasma glucose accompanied by the low insulin concentration is probably one of the major factors accounting for the reduced growth rate. On the other hand, compensatory mechanisms such as increased erythropoiesis results in increased packed cell volume and thus almost normal oxygen content may protect the fetus from hypoxaemia.

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