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THE CARDIOVASCULAR EFFECTS OF CIRCULATING CATECHOLAMINES IN FETAL SHEEP

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SUMMARY

1. Adrenaline and noradrenaline have been infused into the fetal sheep to produce plasma concentrations comparable to those seen during hypoxia and the cardiovascular changes compared with those seen in response to hypoxia. The effect of isoprenaline, methoxamine, and β- and α-adrenergic antagonists were also investigated.

2. There were no significant changes in the blood gas values during any of the infusions except for a mean fall in pH of 0·04 during adrenaline infusion.

3. Adrenaline caused a fall in the fetal heart rate followed by a rise above the control value after 15–20 min. The fall in heart rate was abolished when the rise in blood pressure was blocked with phentolamine. The rise in heart rate was blocked by propranolol. The exact cause of the biphasic changes in heart rate during adrenaline infusion is not clear.

4. A fall in heart rate was not seen with noradrenaline; a small rise was. Propranolol changed this into a fall in heart rate while phentolamine increased the size of the heart rate rise.

5. Phentolamine alone increased the fetal heart rate by 25% and reduced blood pressure by 12%; propranolol alone reduced heart rate by 14% and had no effect on blood pressure. Isoprenaline increased fetal heart rate and reduced blood pressure.

6. The incidence of fetal breathing movements was highly variable. Despite this a significant increase was observed during adrenaline infusion. None of the other infusions had consistent effects.

7. The role of the circulating catecholamines in mediating or modifying the cardiovascular responses to hypoxia in the fetal sheep is discussed.

INTRODUCTION

During fetal development there is a progressive increase in the sympathetic innervation of the tissues (Hökfelt, 1951; Bertler, 1961; Greenberg & Lind, 1961; Kärki, Kuntzman & Brodie, 1962; Iversen, De Complain, Glowinski & Axelrod, 1967; Ignarro & Shideman, 1968*a*; Friedman, Pool, Jacobowitz, Seagren & Braunwald, 1968; Gennser & Nilsson, 1970; Read & Burnstock, 1970; Lebowitz, Novick & Rudolph, 1972; Lipp & Rudolph, 1972; Hyyppä, 1972). The uptake of

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catecholamines by tissues such as the heart is an important part of their inactivation and is related to the density of sympathetic innervation (Iversen, 1967). Together these two facts impart to some of the fetal organs, such as the heart, a supersensitivity to catecholamines (Hall, 1957; McCarty, Lee & Shideman, 1960; Ignarro & Shideman, 1968*b*; Gennser & Nilsson, 1970; Friedman, 1973). Such observations have suggested that circulating catecholamines are relatively more important in fetal than in adult life.

Asphyxia increases the output of adrenaline and noradrenaline from the adrenal of the fetal sheep (Comline & Silver, 1961; Comline, Silver & Silver, 1965) and hypoxia causes a sustained elevation of their plasma concentration (Jones & Robinson, 1975; Jones, 1977). As part of a study on the importance of circulating catecholamines for the fetus we report in this and the succeeding paper, the effects of maintaining, by infusion, elevated plasma catecholamine concentrations comparable to those seen during hypoxia. These are compared with the fetal responses to hypoxia.

METHODS

Animal handling and surgery. The fetuses of sixteen ewes of mixed breeds were studied and their gestational age ranged from 115 to 141 days at the time of experimentation. Ewes bearing either single or twin fetuses were used and in the latter case only one fetus was catheterized. Surgery was carried out on day 110–115 of pregnancy. The ewes were anaesthetized with 1 g Na thiopentone (Abbott Laboratories Ltd., Queenborough, Kent) and anaesthesia was maintained by administration halothane in O_2. The fetal head was delivered through an incision in the uterus and maternal abdomen and the skin of the fetal neck and the uterine wall were clamped to minimize loss of amniotic fluid. Catheters (polyethylene, internal diameter 0·86 mm, external diameter 1·27 mm) were implanted in the fetal carotid artery and jugular vein, with the catheter tips advanced 6–7 cm along the vessel. Similar catheters (polyvinyl chloride, internal diameters 2 mm) had previously been implanted in the maternal blood vessels. A catheter (polyvinyl chloride, internal diameter 2 mm, external diameter 3 mm, with side holes in the distal end) for recording intra-uterine pressure was implanted in the amniotic cavity and attached to the fetal neck. Before closing cut surfaces they were sprayed with an antibiotic powder containing polymixin B, bacitracin and novobiocin (Framyspray, Fisons Ltd., Loughborough). The operating time was approximately 40 min and all ewes recovered promptly after extubation. When recovery from the anaesthetic was complete the ewe was placed in a metabolic cage. An intramuscular injection of 0·5 g streptomycin sulphate (Glaxo Laboratories Ltd., Greenford, Middlesex) was given. Recordings of heart rate, blood pressure, fetal breathing movements and intra-amniotic pressure were made as previously described (Dawes, Fox, Leduc, Liggins & Richards, 1972). All fetuses studied were allowed to recover from the operation for a minimum of 5 days.

Infusion of adrenergic compounds. For the infusions all compounds were dissolved in 0·9% (w/v) NaCl acidified with HCl to pH3 and given at 6·6 ml./hr into the jugular vein. In control experiments the drug was omitted from the infusion saline. Adrenaline, noradrenaline and isoprenaline were each infused at 1·3 μg/min (i.e. about 0·3–0·6 μg/min.kg). The α-mimetic compound methoxamine was infused at 1·0 μg/min (i.e. about 0·3–0·5 μg/min.kg). The α-blocking agent phentolamine was given as a single injection of 1 mg into the fetal jugular vein followed 2 min later by an infusion of 100 μg/min (i.e. about 30–50 μg/min.kg). The β-blocking agent propranolol was given as a single injection of 2 mg into the fetal jugular vein followed 2 min later by an infusion at 44 μg/min (i.e. about 11–22 μg/min.kg). Where catecholamines were given with blocking agents they were administered together in the same infusate. The experimental plan consisted of a 60 min control period, a 60 min infusion period and a post-infusion period of up to 2 hr.

For propranolol the dose required was determined as the minimum infusion rate that would block the rise in heart rate produced by repeated single intravenous injections of 1 μg isoprenaline over 1 hr. For phentolamine it was determined as the minimum infusion rate that

would block the rise in blood pressure produced by single repeated intravenous injections of 1 μg noradrenaline over 1 hr.

Blood gas and pH determination. At 60 and at 10 min before, 30 and 60 min during and 120 min after each infusion 0·7 ml. of fetal and maternal carotid blood was collected into glass syringes for the immediate determination of pH, P_{a,CO_2} and P_{a,CO_2} using a Radiometer Model 27 Acid-Base Analyser.

Determination of plasma catecholamines. In some cases plasma catecholamines were determined as previously described (Jones & Robinson, 1975; Jones & Rurak, 1976). The recovery of 1 ng each of adrenaline and noradrenaline after separation of plasma on Dowex was 73·2 ± 3·2 (22) % and 77·3 ± 4·9 (20) % respectively.

Expression of results. During the experimental period fetal arterial blood pressure, heart rate and breathing movements were recorded continuously. The blood pressure and heart rate means over 5 min periods were calculated. Where appropriate results are expressed as means ± S.E. with the number of observations in parentheses. Statistical significance has been determined by the Student's *t* test.

TABLE 1. Summary of the experimental plan

Infusion	Infusion conditions	Fetal age range	No. of fetuses	No. of experiments
Adrenaline	1·3 μg/min (0·3–0·6 μg/min.kg)	117–135	5	13
Adrenaline plus propanolol	Propranolol, 2 mg injection, then infusion 2 min later at 44 μg/min plus adrenaline at 1·3 μg/min	115–137	4	6
Adrenaline plus phentolamine	Adrenaline at 7·3 μg/min of phentolamine, 1 mg injection, then infusion 2 min later at 100 μg/min plus adrenaline at 1·3 μg/min	120–131	3	6
Noradrenaline	As for adrenaline	121–134	3	5
Noradrenaline plus propranolol	As for adrenaline	122–134	3	5
Noradrenaline plus phentolamine	As for adrenaline	123–131	3	3
Propranolol	2 mg injection then infusion 2 min later at 44 μg/min	124–134	2	2
Phentolamine	1 mg injection then infused 2 min later at 100 μg/min	124–133	3	3
Isoprenaline	As for adrenaline	124–127	4	6
Isoprenaline plus propranolol	As for adrenaline	124–127	3	4
Methoxamine	1·0 μg/min (0·3–5 μg/min.kg)	126–128	3	4

RESULTS

Experimental plan

The experimental plan for the different infusions is outlined in Table 1. Where more than one infusion was given to one fetus a minimum period of 48 hr was allowed between infusions and no significant differences were noted in any measurements made in the different control or experimental periods. No significant differences were noted in the responses of fetuses from single or twin pregnancies. Similarly no significant differences were noted in the response of the fetuses over the age ranges studied (Table 1).

Catecholamine concentration

The plasma catecholamine concentrations in fetuses prior to infusion were not detectable, i.e. < 0·1 ng/ml. During the infusions they rose to values similar to those previously reported (Jones & Robinson, 1975). Neither phentolamine nor propranolol infused with the catecholamine had an effect on the steady-state concentration achieved (Table 2) and on infusion of the blocking agents or methoxamine alone the plasma catecholamine concentrations were still < 0·1 ng/ml.

TABLE 2. Plasma catecholamine concentration in fetal sheep

Infusion	No.	Adrenaline (ng/ml.)	Noradrenaline (ng/ml.)
Adrenaline	7	2·7 ± 1·3	< 0·1
Adrenaline plus phentolamine	3	3·1 (± 1·9)	< 0·1
Adrenaline plus propranolol	3	2·2 (± 1·5)	< 0·1
Noradrenaline	3	< 0·1	4·2 (± 2·3)
Noradrenaline plus phentolamine	2	< 0·1	4·7 (± 1·6)

The values represent catecholamine concentrations ± S.D. from plasma obtained at the end of the 60 min infusion period.

Fetal arterial blood gas and pH values

There were no significant changes in P_{a,O_2} or P_{a,CO_2} in mother or fetus during any of the infusions. Mean maternal and fetal P_{a,O_2} values during the control period were 99·5 ± 1·0 (73) and 24·1 ± 0·4 (85) mmHg respectively, while the corresponding P_{a,CO_2} values were 33·2 ± 0·4 (71) and 47·9 ± 0·5 (86) mmHg respectively.

The mean carotid arterial pH of all the fetuses before the infusion was 7·35 ± 0·006 (87). During adrenaline infusion only was there a change in pH, which fell to 7·32 ± 0·009 (n = 12, P < 0·01) by 30 min and to 7·31 ± 0·01 (n = 13, P < 0·01) by 60 min. The maternal blood pH did not change during any of the infusions and its mean value during the control period was 7·43 ± 0·009 (74).

Heart rate and blood pressure

Adrenaline infusion. Before the infusion the mean fetal heart rate was 189 ± 7 (13) beats/min. This fell during the first 10 min of the infusion to about 155 beats/min then rose (Fig. 1*A*). The heart rate during the second 30 min was 220 ± 8 (13) beats/min which is 18·4 ± 3 (13) % higher than the mean control value (P < 0·001). Blood pressure rose from 38·3 ± 1·1 (13) mmHg to 45·8 ± 1·3 (13) mmHg (P < 0·001) within 10 min of starting the infusion (Fig. 1*D*). Propranolol infusion blocked the rise in heart rate produced by adrenaline, although the initial fall still occurred (Fig. 1*B*), while the change in blood pressure was unaffected (Fig. 1*E*). Phentolamine abolished the initial fall in heart rate caused by adrenaline (Fig. 1*C*) and increased the subsequent rise in heart rate to 249 ± 9 (6) beats/min. This was an increase of 41·8 ± 5·8 (6) % (P < 0·001) over the control period and was significantly larger (P < 0·005) than with adrenaline alone or with phentolamine alone (Fig. 4). Phentolamine converted the adrenaline-induced rise in blood pressure into a fall of 10·2 ± 4·5 (6) % (Fig. 1*F*).

Noradrenaline infusion. Before infusion the fetal heart rate was 189 ± 15 (5) beats/min and rose to 209 ± 9 (5) beats/min during the second 30 min of the infusion (Fig. 2*A*). This was an increase of 10·6 ± 3·7 (5) % ($P < 0·05$). There was no evidence of a fall in heart rate during the initial stages of the infusion. An increase in blood pressure of 18·2 ± 4·4 (5) % ($P < 0·01$) occurred (Fig. 2*D*). Propranolol blocked the rise in heart rate caused by noradrenaline (Fig. 2*B*) while phentolamine did not (Fig. 2*C*). The rise in blood pressure was blocked by phentolamine (Fig. 2*F*) but not by propranolol (Fig. 2*E*).

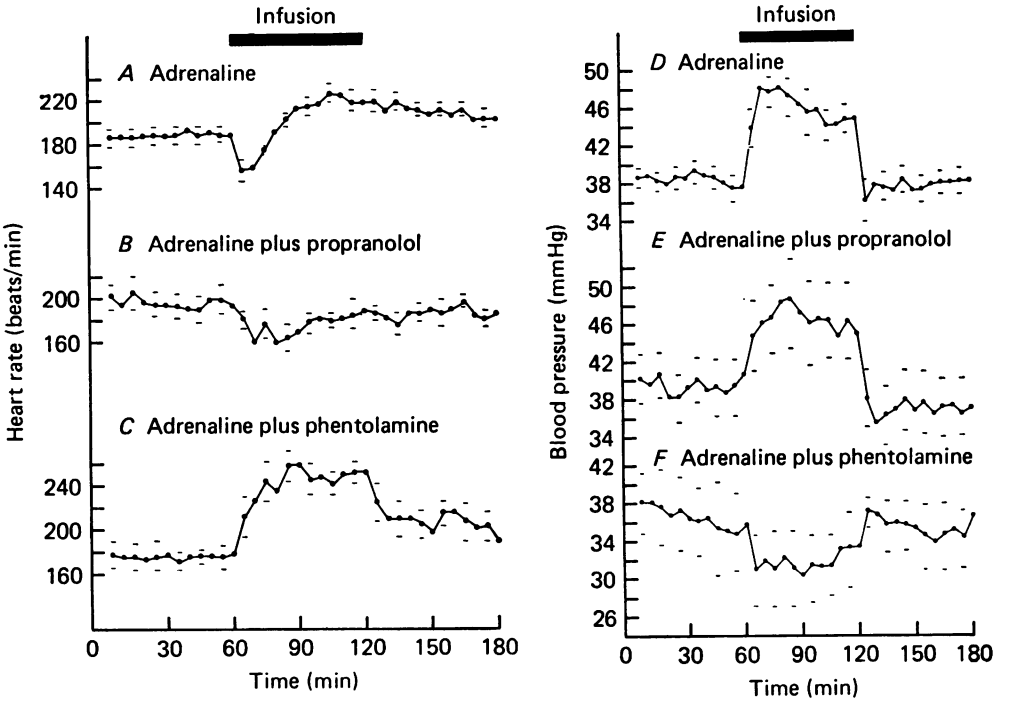

Fig. 1. The changes in fetal heart rate (*A–C*) and blood pressure (*D–F*) during the infusion of (A, D) adrenaline, (*B*, *E*) adrenaline plus propranolol (C, F) adrenaline plus phentolamine as outlined in Table 1. The spaces between the horizontal bars represent 2 S.E. of means.

Infusion of sympathomimetic amines. Isoprenaline infusion increased the heart rate from 167 ± 2 (6) beats/min to 293 ± 3 (6) beats/min (Fig. 3*A*) which was an increase of 75·1 ± 1·5 (6) % ($P < 0·001$). Blood pressure fell by 10·9 ± 1·4 (6) % ($P < 0·002$) during the infusion. Propranolol completely blocked the rise in heart rate (Fig. 3*B*) and prevented the fall in blood pressure.

Methoxamine infusion had no significant effect on fetal heart rate or blood pressure.

Infusion of blocking agents. The infusion of phentolamine alone caused a rise in fetal heart rate (Fig. 4) of 24·7 ± 3·2 (3) % ($P < 0·02$), while the blood pressure fell by 11·7 ± 2·2 (3) %.

Propranolol alone caused a 14 % fall in the heart rate but little change in blood pressure (Fig. 4).

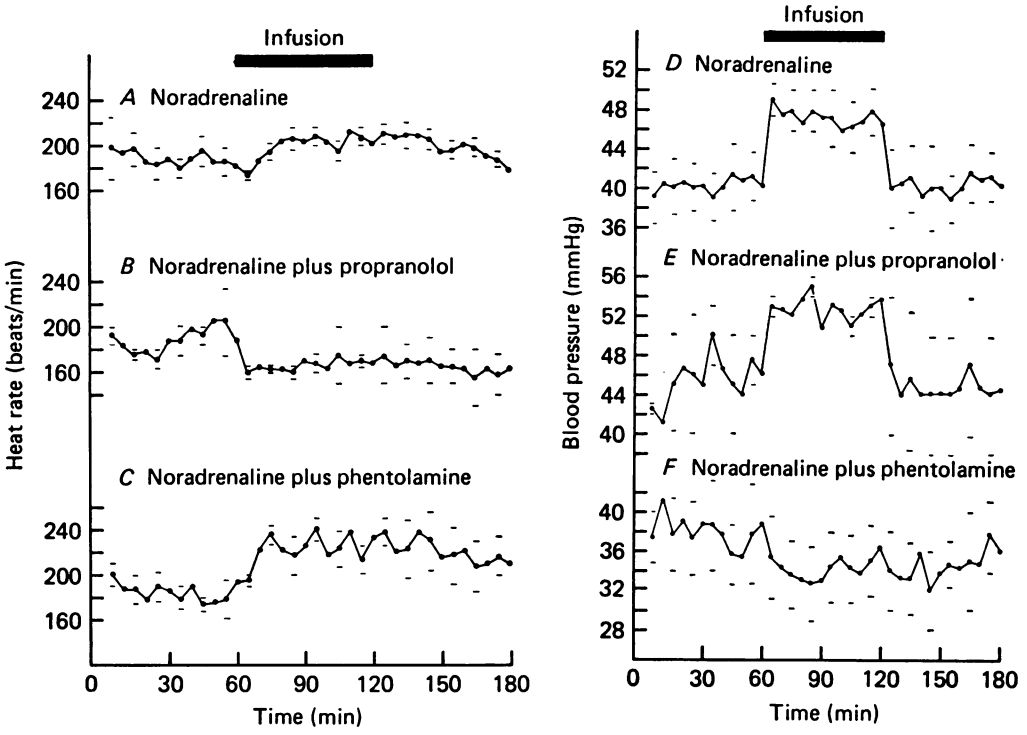

Fig. 2. The changes in fetal heart rate (*A–C*) and blood pressure (*D–F*) during the infusion of *A*, *D*) noradrenaline, (*B*, *E*) noradrenaline plus propranolol, (*C*, *F*) noradrenaline plus phentolamine as outlined in Table 1. The spaces between the horizontal bars represent 2 S.E. of means.

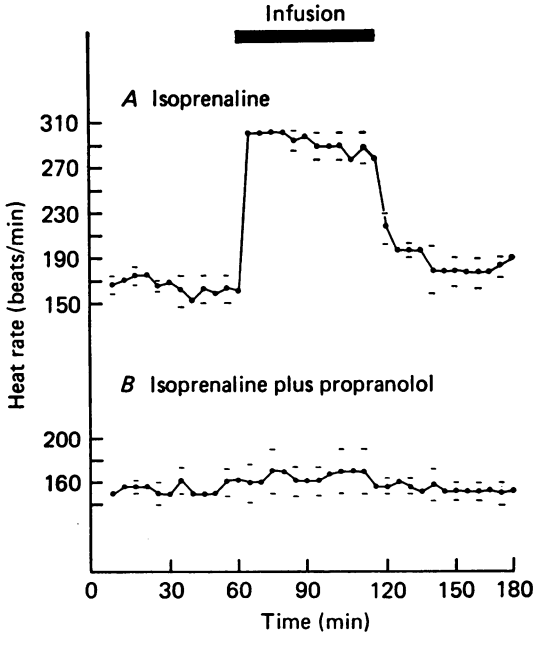

Fig. 3. The changes in fetal heart rate during the infusion of (A) isoprenaline, (B) isoprenaline plus propranolol as outlined in Table 1. The spaces between the horizontal bars represent 2 S.E. of means.

Controls. When the vehicle used to administer the adrenergic compounds, 0·9% NaCl (pH3), was infused alone into the jugular vein of six fetal sheep there were no consistent changes in heart rate or blood pressure.

The fetal heart rate showed an interesting linear relationship (correlation coefficient, $r = 0{\cdot}6$, $P < 0{\cdot}01$) with the blood glucose concentration observed during the control period (Fig. 5).

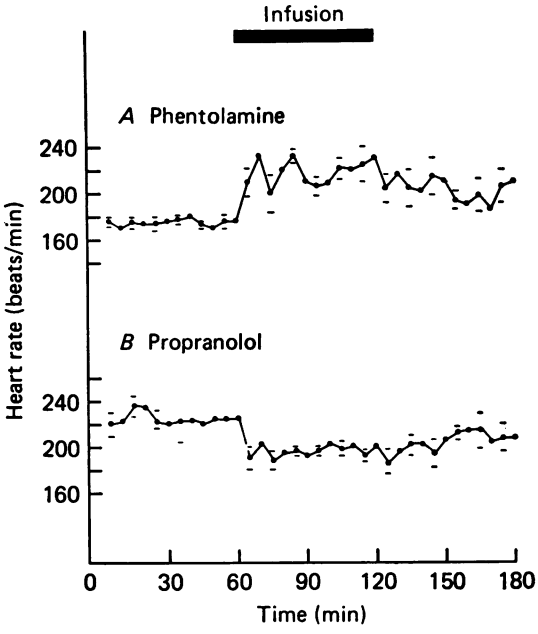

Fig. 4

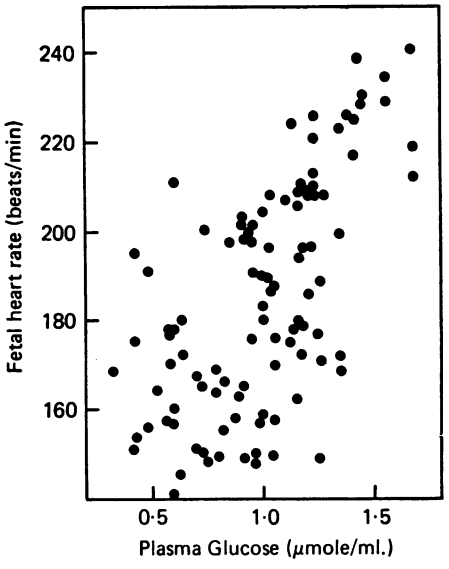

Fig. 5

Fig. 4. The changes in fetal heart rate during the infusion of (*A*) phentolamine, (*B*) propranolol as outlined in Table 1. The space between the horizontal bars represent 2 S.E. of means.

Fig. 5. The relationship between the resting fetal heart rate and plasma glucose concentration (correlation coefficient = 0·6, $P < 0{\cdot}01$). The age range of the fetuses studied was 115–137 days.

TABLE 3. The effect of catecholamines on fetal breathing movements

		Fetal breathing movements, %/hr		
Infusion	No.	Control 0–60 min	Infusion 60–120 min	Post-infusion 120–180 min
Adrenaline	13	24·1 ± 18·2	40·6 ± 14·6*	19·5 ± 17·3
Noradrenaline	5	25·4 ± 26·2	48·2 ± 8·5	24·3 ± 23·2
Adrenaline plus phentolamine	6	17·9 ± 13·4	52·2 ± 35·3	25·0 ± 29·9
Adrenaline plus propranolol	6	17·8 ± 12·4	31·1 ± 18·8	13·3 ± 16·5

Fetal breathing movements are expressed as the percentage of the times/hr that breathing movements are present ± S.D. Level of significance compared with the control period: *$P < 0{\cdot}02$.

Fetal breathing movements

Adrenaline infused into the fetal sheep increased the incidence of fetal breathing movements (Table 3). This effect was variable, in nine of the fetus there was an increase while in four no change was observed. The mean increase with adrenaline was $16{\cdot}9 \pm 11{\cdot}5$ (13) %/hr ($P < 0{\cdot}001$). The effect of adrenaline, when present, was normally seen 10–15 min after starting the infusion (Fig. 6). With the other infusions the variability was too large to determine a statistically significant response (Table 3).

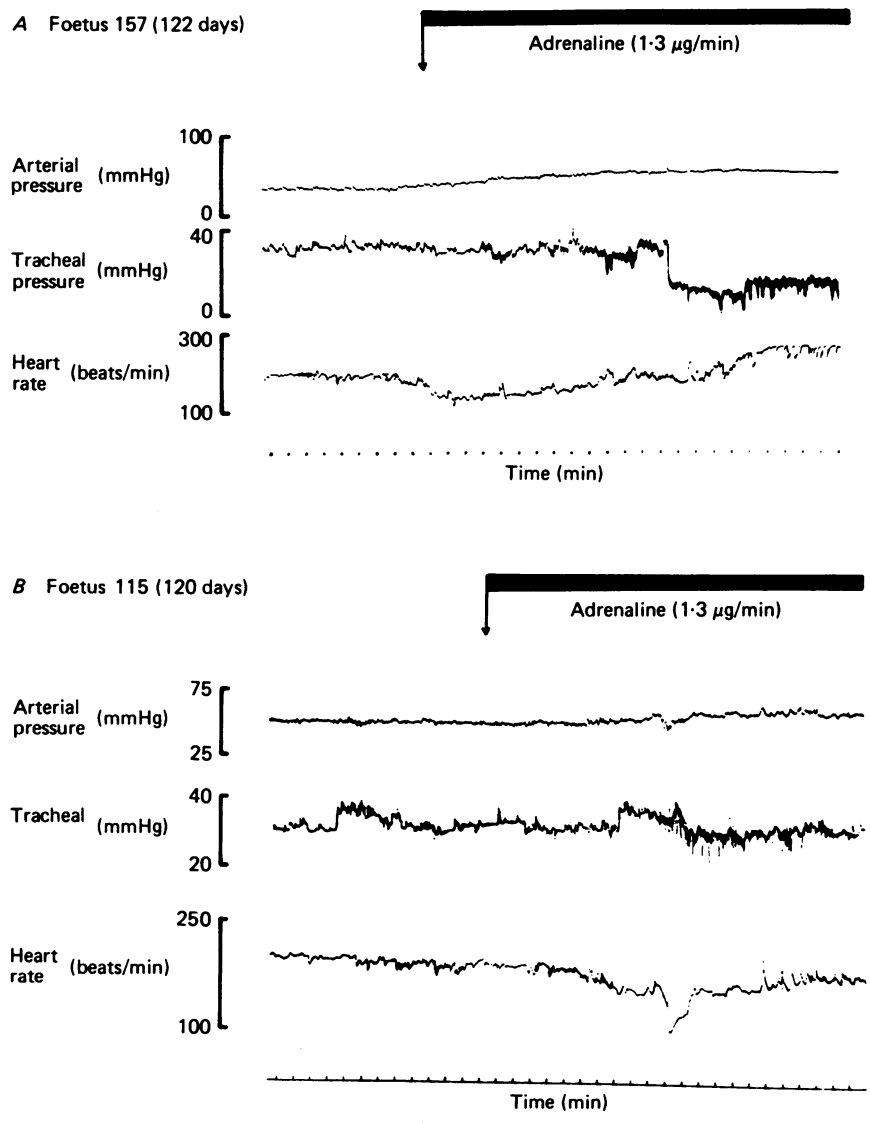

Fig. 6. The changes in arterial pressure, tracheal pressure and heart rate in response to the infusion of adrenaline (1·3 μg/min) into (*A*) fetus 157 of 122 days, (*B*) fetus 115 of 120 days.

DISCUSSION

The fetal sheep, removed from the uterus but with an intact placental circulation and normal blood gas values, has a very high plasma catecholamine concentration (Jones & Rurak, 1976). It is at least 200 times higher than normal, at least 5 times higher than in these infusion experiments, and values as high are not usually observed in hypoxic fetus except under pathological conditions (Jones & Robinson, 1975; Jones, 1977). Thus many of the studies involving the use of the exteriorized fetus must be interpreted with caution and the effects of circulating catecholamines can only be satisfactorily quantified with the fetus *in utero*.

The cardiovascular responses to single injections of large quantities of adrenaline or of noradrenaline have been known for many years (Barcroft & Barron, 1945; Dawes, Mott & Rennick, 1956) and have recently been confirmed with the injection of somewhat smaller quantities (0·75–3·0 μg/kg) in unaesthetized fetal sheep *in utero* (Joelsson, Barton, Daniel, James & Adamsons, 1972). There is a rise in blood pressure and a fall in heart rate that is prevented by vagotomy. This is associated with an increase in peripheral and pulmonary resistance (Assali, Holm & Sehgal, 1962; Cassin, Dawes & Ross, 1964; Dawes, Lewis, Milligan, Roach & Talner, 1968) and an increase in umbilical and carotid blood flow (Assali *et al.* 1962). Although there are conflicting reports on whether single injections of noradrenaline either increase (Assali *et al.* 1962) or decrease (Dawes *et al.* 1968) femoral artery blood flow. While these studies, in most instances, give a qualitative indication of the cardiovascular changes caused by circulating catecholamines they are not a reliable indicator of the quantitative nature of the changes during physiological elevations of plasma catecholamine concentration. The importance of adequately controlling the plasma catecholamine concentration when studying its effects is shown by the biphasic action of adrenaline first increasing muscle flow at low infusion rates and then reducing it at somewhat higher infusion rates (Celander, 1954; Chalmers, Korner & White, 1966).

In the fetus conditions which stimulate the secretion of catecholamines such as hypoxia (Jones & Robinson, 1975; Jones, 1977) or labour (Lagercrantz & Bistoletti, 1977) do not produce transient changes but maintain an elevated plasma concentration.

The well defined fall in heart rate that occurs after adrenaline injection into fetal sheep clearly also occurs when the plasma adrenaline concentration is raised to values similar to those seen during hypoxia. The fall is maximal at the time (10 min) when based on the half-life of adrenaline (Jones & Robinson, 1975) the steady-state concentration should be achieved. However, the fall in heart rate is only transient, in contrast to the situation in hypoxia where the fetal heart rate may remain depressed (Jones & Robinson, 1975), and is followed by a rapid rise. The abolition by phentolamine of the fall in heart rate is consistent with the view that it is a reflex response to the rise in blood pressure. The subsequent rise in heart rate during the adrenaline infusion is clearly a β-effect and probably largely the result of the β-actions of adrenaline overcoming the inhibition of the heart by parasympathetic efferent vagal fibres. It could be caused by a reduction in the activity of parasympathetic efferent vagal fibres. Although if the fetus behaves like the adult, this is unlikely

to be the result of reduced baroreceptor activity as in the adult they reset relatively slowly (Krieger, 1970) and catecholamines (Heymans & Van Den Huevel-Heymans, 1950; Landgren, Neil & Zotterman, 1952) and possibly the activity of sympathetic innervating fibres increase their firing rate (Koizumi & Sato, 1969). The nature of the adrenaline effect on the heart rate and the suggested ability of high circulating catecholamines to overcome the vagal inhibition of the heart induced by hypoxia (Jones & Robinson, 1975) indicates that circulating catecholamines may, in some situations, be important determinants of fetal heart rate and explain why in a previous study with the fetal sheep the heart rate returned to normal during hypoxia (Boddy, Dawes, Fisher, Pinter & Robinson, 1974).

The magnitude of the effects of noradrenaline are consistent with it being substantially less active than adrenaline at equimolar concentrations (Malmejac, 1964) and were similar to that observed on infusion into adult dogs (Laks, Callis & Swan, 1971). In contrast to the work described above, in which single injections were given, noradrenaline caused no clear initial fall in heart rate. However, the effects of phentolamine indicated that during noradrenaline infusion there was an increase in baroreceptor reflex inhibition of the heart rate. This probably explains why, compared to the relative β-potencies of the two compounds (Furchgott, 1967), isoprenaline caused much larger changes in heart rate than noradrenaline. Also between 120 and 140 days the sympathetic innervation of the heart becomes well developed (Lebowitz *et al.* 1972) and this would further reduce the effectiveness of exogenous noradrenaline.

It has been suggested that the fetus is less sensitive to circulating catecholamines than the adult (Dornhorst & Young, 1952; Assali *et al.* 1962). The present results do not support this view. Infusion of adrenaline into ewes at similar rates to those used produced little or no effect on blood pressure and the rise in heart rate was not much greater than fetal response, and less than that in the fetuses in which increase in blood pressure was blocked (Jones & Robinson, 1975; Rosenfeld, Barton & Meschia, 1976).

The effects of the α- and β-blocking agents alone were similar to those previously reported for single injections into fetal sheep *in utero* (Vapaavouri, Shinebourne, Williams, Heymann & Rudolph, 1973; Nuwayhid, Brinkman, Su, Bevan & Assali, 1975) and indicate that at the age of the fetuses studied here there is, in the 'resting' condition, substantial activity in the inhibitory vagal fibres to the heart (cf. the effects of atropine: Vapaavouri *et al.* 1975; Ikenoue, Quilligan & Murata, 1976). Studies with sympathomimetic compounds have indicated that β-stimulation is associated with an increase in heart and umbilical blood flow and α-stimulation may cause a fall in flow to the heart, kidney, and in flow in the umbilical vein (Barrett, Heyman & Rudolph, 1972).

Thus, in summary, during physiological elevation of plasma adrenaline or noradrenaline concentration there is a β-stimulation of the heart which may or may not (particularly before 110 days, Shinebourne, Vapaavouri, Williams, Heymann & Rudolph, 1972; Boddy *et al.* 1974) be overcome by increased parasympathetic efferent vagal activity associated with the increased blood pressure and peripheral resistance. It is unlikely that umbilical blood flow falls, particularly as there are no changes in blood gas tensions. Since this represents about 50 % of the cardiac output,

peripheral blood flow, in the initial stages of the adrenaline infusion and throughout the noradrenaline infusion, is likely to fall substantially. Provided cardiac output increases with increasing heart rate (Rudolph & Heymann, 1973) peripheral perfusion should increase from a low value during the first 10–15 min of the adrenaline infusion. Thus the biphasic nature of the responses to adrenaline may be to ensure that the period of severely reduced peripheral blood flow is relatively short. The same argument could apply to the responses seen during hypoxia and in cases where the fetus is deteriorating the increased heart rate may be required to increase the proportion of the cardiac output going to the placenta (Cohn, Sacks, Heymann & Rudolph, 1974; Jones & Robinson, 1975). The mechanism of inducing biphasic changes in heart rate and by which peripheral perfusion is increased is probably complex. After initial vasoconstriction there is likely to be vasodilatation of metabolic origin (Korner, 1974). In addition peripheral chemoreceptor action or central adrenergic effects could modulate, in the brain, the magnitude of the baroreceptor reflex and the sympathetic stimulation of the heart (Korner, 1971). During hypoxia the rise in plasma catecholamines may be secondary to and reinforce, rather than initiate, these changes, although during adrenaline infusion it is likely to have an initiating role. The responses in the hypoxic fetal sheep are somewhat less clear than in, for instance, the hypoxic adult rabbit, as the arterial pressure in the sheep tends to progressively rise during the course of hypoxia (Boddy *et al.* 1974; Jones & Robinson, 1975) rather than rapidly rise then fall as in the rabbit (Korner & Uther, 1969). Depression of the fetal heart rate is occasionally seen late in pregnancy (Swartwout, Campbell & Williams, 1961) and this is probably associated with increased catecholamine secretion (Lagercrantz & Bistoletti, 1977).

The effect of adrenaline on fetal breathing contrasts with that of hypoxaemia where the breathing movements disappear (Boddy *et al.* 1974). The increase induced by adrenaline infusion may have been caused by an increase in the cerebral blood flow (Assali *et al.* 1962). One of the striking features of this effect was that in a significant proportion of the infusions there was no response to adrenaline. This made the analysis of the actions of the blocking agents and of noradrenaline difficult. A similar variability has been noted in the sensitivity of fetal breathing movements to nerve stimulation (Chapman, Dawes, Rurak & Wilds, 1977).

The fairly close relationship between heart rate and plasma glucose concentration is surprising when considering all the factors likely to affect the heart rate. It may result from a high permeability of the fetal heart to glucose at a time of insulin insensitivity (Clark, 1971), although it must be remembered that the K_m for glucose of the hexokinase in fetal heart is much less than the plasma glucose concentration (Faulkner & Jones, 1976). This correlation is all the more surprising as hypoglycaemia would be expected to increase the secretion of adrenal catecholamines.

REFERENCES

ASSALI, N. S., HOLM, L. W. & SEHGAL, N. (1962). Regional blood flow and vascular resistance of the fetus in utero. Action of vasoactive drugs. *Am. J. Obstet. Gynec.* **83**, 809–817.

BARCROFT, J. & BARRON, D. H. (1945). Blood pressure and pulse rate in the foetal sheep. *J. exp. Biol.* **22**, 63–74.

BARRETT, C. T., HEYMANN, M. A. & RUDOLPH, A. M. (1972). Alpha and beta adrenergic receptor activity in fetal sheep. *Am. J. Obstet. Gynec.* **112**, 1114–1121.

BERTLER, A. (1961). Occurrence and localisation of catechol amines in the human brain. *Acta physiol. scand.* **51**, 97–107.

BODDY, K., DAWES, G. S., FISHER, R., PINTER, S. & ROBINSON, J. S. (1974). Foetal respiratory movements, electrocortical and cardiovascular responses to hypoxaemia and hypercapnia in sheep. *J. Physiol.* **243**, 599–618.

CASSIN, S., DAWES, G. S. & ROSS, B. B. (1964). Pulmonary flow and vascular resistance in immature foetal lambs. *J. Physiol.* **171**, 80–89.

CELANDER, O. (1954). The range of control exercised by the sympathico-adrenal system. *Acta physiol. scand.* **32**, Suppl. 116, 1–132.

CHALMERS, J. P., KORNER, P. I. & WHITE, S. W. (1966). The control of the circulation in skeletal muscle during arterial hypoxia in the rabbit. *J. Physiol.* **184**, 698–716.

CHAPMAN, R. L. K., DAWES, G. S., RURAK, D. W. & WILDS, P. L. (1977). Foetal breathing and peripheral nerve stimulation *in utero*. *J. Physiol.* **272**, 13–14P.

CLARK, C. M. (1971). Carbohydrate metabolism in the isolated fetal rat heart. *Am. J. Physiol.* **220**, 583–588.

COHN, H. E., SACKS, E. J., HEYMANN, M. A. & RUDOLPH, A. M. (1974). Cardiovascular responses to hypoxaemia and acidemia in fetal lambs. *Am. J. Obstet. Gynec.* **120**, 817–824.

COMLINE, R. S. & SILVER, M. (1961). The release of adrenaline and noradrenaline from the adrenal glands of the foetal sheep. *J. Physiol.* **156**, 424–444.

COMLINE, R. S., SILVER, I. A., & SILVER, M. (1965). Factors responsible for the stimulation of the adrenal medulla during asphyxia in the foetal lamb. *J. Physiol.* **178**, 211–238.

DAWES, G. S., FOX, H. E., LEDUC, B. M., LIGGINS, G. C. & RICHARDS, R. T. (1972). Respiratory movements and rapid eye movement sleep in the foetal lamb. *J. Physiol.* **220**, 119–143.

DAWES, G. S., LEWIS, B. V., MILLIGAN, J. E., ROACH, M. R. & TALNER, N. S. (1968). Vasomotor responses in the hind limbs of foetal and new-born lambs to asphyxia and aortic chemoreceptor stimulation. *J. Physiol.* **195**, 55–81.

DAWES, G. S., MOTT, J. C. & RENNICK, B. R. (1956). Some effects of adrenaline, noradrenaline and acetylcholine on the foetal circulation in the lamb. *J. Physiol.* **134**, 139–148.

DORNHORST, A. C. & YOUNG, I. M. (1952). The action of adrenaline and noradrenaline on the placental and foetal circulation in rabbit and guinea-pig. *J. Physiol.* **118**, 282–288.

FAULKNER, A. & JONES, C. (1976). Hexokinase isoenzymes in tissues of the adult and developing guinea-pig. *Arch. Biochem. Biophys.* **175**, 477–486.

FRIEDMAN, W. F. (1973). In *Neonatal Heart Disease*, ed. FRIEDMAN, W. F., LESCH, M. D. & SONNENBLICK, H., pp. 21–49. New York: Grune & Stratton, Inc.

FRIEDMAN, W. F., POOL, P. E., JACOBOWITZ, D., SEAGREN, S. C. & BRAUNWALD, E. (1968). Sympathetic innervation of the developing rabbit heart. Biochemical and histological comparisons of foetal and neonatal myocardium. *Circulation Res.* **23**, 25–32.

FURCHGOTT, R. F. (1967). The pharmacological differentiation of adrenergic receptors. *Ann. N.Y. Acad. Sci.* **139**, 553–570.

GENNSER, G. & NILSSON, E. (1970). Response to adrenaline, acetylcholine and change of contraction frequency in early human foetal hearts. *Experentia* **26**, 1105–1107.

GREENBERG, R. E. & LIND, J. (1961). Catecholamines in tissues of the human fetus. *Pediatrics, Springfield* **27**, 904–911.

HALL, E. K. (1957). Acetylcholine and epinephrine effects on the embryonic rat heart. *J. cell. comp. Physiol.* **49**, 187–200.

HEYMANS, C. & VAN DEN HUEVEL-HEYMANS, G. (1950). Action of drugs on arterial wall of carotid sinus and blood pressure. *Archs Int. Pharmacol.* **83**, 520.

HÖKFELT, B. (1951). Noradrenaline and adrenaline in mammalian tissues. *Acta. physiol. scand.* **25**, Suppl. 92.

HYYPPÄ, M. (1972). Hypothalamic monoamines in human fetuses. *Neuroendocrinology* **9**, 257–266.

IGNARRO, L. J. & SHIDEMAN, F. E. (1968*a*). Appearance and concentrations of catecholamines and their biosynthesis in the embryonic and developing chick. *J. Pharmac. exp. Ther.* **159**, 38–48.

IGNARRO, L. J. & SHIDEMAN, F. E. (1968*b*). Norepinephrine and epinephrine in the embryo and embryonic heart of the chick: uptake and subcellular distribution. *J. Pharmac. exp. Ther.* **159**, 49–58.

IKENOUE, T., QUILLIGAN, E. J. & MURATA, Y. (1976). Circulatory response to atropine in sheep fetus. *Am. J. Obstet. Gynec.* **126**, 253–260.

IVERSEN, L. L. (1967). *The Uptake and Storage of Noradrenaline*. Cambridge: University Press.

IVERSEN, L. L., DE COMPLAIN, J., GLOWINSKI, J. & AXELROD, J. (1967). Uptake, storage and metabolism of norepinephrine in tissues of the developing rat. *J. Pharmac. exp. Ther.* **157**, 509–516.

JOELSSON, J., BARTON, M. D., DANIEL, S., JAMES, S. & ADAMSONS, K. (1972). The response of the unanesthetized sheep fetus to sympathomimetic amines and adrenergic blocking agents. *Am. J. Obstet. Gynec.* **114**, 43–50.

JONES, C. T. (1977). The development of some metabolic responses to hypoxia in the foetal sheep. *J. Physiol.* **265**, 743–762.

JONES, C. T. & ROBINSON, R. O. (1975). Plasma catecholamines in foetal and adult sheep. *J. Physiol.* **248**, 15–33.

JONES, C. T. & RURAK, D. (1976). The distribution and clearance of hormones and metabolites in the circulation of the foetal sheep. *Q. Jl exp. Physiol.* **61**, 287–295.

KÄRKI, N., KUNTZMAN, R. & BRODIE, B. B. (1962). Storage, synthesis and metabolism of monoamines in the developing brain. *J. Neurochem.* **9**, 53–58.

KOIZUMI, K. & SATO, A. (1969). Influence of sympathetic innervation on carotid sinus baroreceptor activity. *Am. J. Physiol.* **216**, 321–329.

KORNER, P. I. (1971). Integrative neural cardiovascular control. *Physiol. Rev.* **51**, 312–367.

KORNER, P. I. (1974). In *Physiology Series One*, vol. 1, *Cardiovascular Physiology*, ed. GUYTON, A. C. & JONES, C. E., pp. 163–195. Lancaster: MTP Medical and Technical Publishing Co. Ltd.

KORNER, P. I. & UTHER, M. B. (1969). Dynamic characteristics of the cardiovascular autonomic effects during severe arterial hypoxia in the unanaesthetized rabbit. *Circulation. Res.* **24**, 671–687.

KRIEGER, E. M. (1970). Time course of baroreceptor reseting in acute hypertension. *Am. J. Physiol.* **218**, 486–490.

LAGERCRANTZ, H. & BISTOLETTI, P. (1977). Catecholamine release in the newborn infant at birth. *Pediat. Res.* **11**, 889–893.

LAKS, M., CALLIS, G. & SWAN, H. J. C. (1971). Hemodynamic effects of low doses of norepinephrine in the conscious dog. *Am. J. Physiol.* **220**, 171–173.

LANDGREN, S., NEIL, E. & ZOTTERMAN, Y. (1952). The response of carotid baroreceptors to local administration of drugs. *Acta physiol. scand.* **25**, 24–37.

LEBOWITZ, E. A., NOVICK, J. S. & RUDOPLH, A. M. (1972). Development of myocardial sympathetic innervation in the fetal lamb. *Pediat. Res.* **6**, 887–893.

LIPP, J. A. M. & RUDOLPH, A. M. (1972). Sympathetic nerve development in the rat and guinea-pig heart. *Biologia neonat.* **21**, 76–82.

MALMEJAC, J. (1964). Activity of the adrenal medulla and its regulation. *Physiol. Rev.* **44**, 186–218.

MCCARTY, L. P., LEE, W. C. & SHIDEMAN, F. E. (1960). Measurement of the ionotropic effects of drugs on the innervated and noninnervated embryonic chick heart. *J. Pharmac. exp. Ther.* **129**, 315–321.

NUWAYHID, B., BRINKMAN, C. R., SU, C., BEVAN, J. A. & ASSALI, N. S. (1975). Development of autonomic control of fetal circulation. *Am. J. Physiol.* **228**, 337–344.

READ, J. B. & BURNSTOCK, G. (1970). Development of the adrenergic innervation and chromaffin cells in the human fetal gut. *Devl Biol.* **22**, 513–534.

ROSENFIELD, C. R., BARTON, M. D. & MESCHIA, G. (1976). Effects of epinephrine on distribution of blood flow in the pregnant ewe. *Am. J. Obstet. Gynec.* **124**, 156–163.

RUDOLPH, A. M. & HEYMANN, M. A. (1973). In *Foetal and Neonatal Physiology*, ed. COMLINE, R. S., CROSS, K. W., DAWES, G. S. & NATHANIELSZ, P. W., pp. 89–111. Cambridge: University Press.

SHINEBOURNE, E. A., VAPAAVOURI, E. K., WILLIAMS, R. L. HEYMANN, M. A. & RUDOLPH, A. M. (1972). Development of baroreflex activity in unaesthetized fetal and neonatal lambs. *Circulation Res.* **31**, 710–718.

SWARTWOUT, J. R., CAMPBELL, W. E. & WILLIAMS, L. G. (1961). Observations on the fetal heart rate. *Am. J. Obstet. Gynec.* **82**, 301–303.

VAPAAVOURI, E. K., SHINEBOURNE, E. A., WILLIAMS, R. L., HEYMANN, M. A. & RUDOLPH, A. M. (1973). Development of cardiovascular responses to autonomic blockade in intact fetal and neonatal lambs. *Biologia Neonat.* **22**, 177–188.