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SOME EFFECTS OF ADRENALINE, NORADRENALINE AND ACETYLCHOLINE ON THE FOETAL CIRCULATION IN THE LAMB

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In the mature foetal lamb most of the blood which reaches the coronary arteries comes from the inferior vena cava through the foramen ovale. A substance injected into a femoral vein will be carried up into the inferior vena cava, and be diluted with a large quantity of blood returning from the placenta; about two-thirds will pass to the left atrium, and one-third to the right atrium (Dawes, Mott & Widdicombe, 1954). The two-thirds which passes into the left atrium will be still further diluted with blood returning from the lungs, and will then be ejected from the left ventricle into the aorta, whence a small fraction may reach the coronary vessels. But a substance injected into a jugular vein will not reach the coronary arteries until it has passed through the lungs, the placenta or the lower part of the foetus.

These considerations led to the hypothesis that substances such as adrenaline and acetylcholine, which are readily destroyed in animal tissues, should have a different effect upon the foetal heart rate and blood pressure according to the route of injection. This paper describes observations which were made to test this hypothesis in lambs of different gestational ages, and also describes some effects of sympathetic amines upon umbilical blood flow.

METHODS

Fifteen mature foetal lambs (>132 days gestation) and ten immature foetal lambs (67–110 days gestation) were used. Pregnant ewes, mainly of a Clun-Hampshire cross-breed, but including a few Kerry Hill, were anaesthetized with sodium pentobarbitone. The initial intravenous injection was supplemented by an intravenous infusion of about 10–20 mg/kg/hr, sufficient to keep both ewe and lamb lightly anaesthetized. The lamb was delivered by Caesarean section and laid on a small warm table so arranged that the umbilical cord was not under tension.

The blood pressure of the ewe was recorded by a mercury manometer from a carotid artery. The blood pressure of the foetus was recorded by a condenser manometer from a femoral artery. In the

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smallest foetuses (about 100 g at 70 days gestation age) the catheters used were so small that the frequency response of the manometer assembly was less than 100 c/s. We were, however, primarily interested in changes in mean pressure. Foetal heart rate was measured from condenser manometer records which had been photographed from an oscilloscope, or were recorded on a direct writing instrument (Cambridge Instrument Co., 3 C.R. 1). In many experiments the voltage output of the condenser manometer was amplified and used to trip an impulse counter (Thorp, 1948), at each pulse wave, so as to give a continuous record of heart rate on a kymograph. In other experiments heart rate was plotted from a meter (Wyatt, 1956).

Umbilical blood flow was measured by inserting a density flowmeter (Dawes, Mott & Vane, 1953) into the common umbilical vein of mature foetal lambs. The time for a known quantity of blood to pass through was recorded on a kymograph by an interval timer (Gaddum & Kwiatkowski, 1938). At the beginning of the preparation the ewe was given O_2 to breathe. The foetal abdomen was opened to the left of the mid-line, and the incision was extended across the mid-line above the umbilicus, so as to expose the common umbilical vein. Heparin (10 mg/kg) was injected intravenously into the foetus, and the right external jugular vein was cannulated. The placental end of the common umbilical vein was then cannulated and rapidly joined by a flexible tube to the external jugular vein. In this way the supply of oxygen to the foetus was interrupted for only a short while, so that in many preparations the heart did not slow, and there was only a small temporary fall of blood pressure. The hepatic end of the common umbilical vein was then cannulated at leisure and joined, through the flowmeter, to the placental end. The flowmeter and tubes were filled with warm dextran solution.

While this method has its disadvantages, it has the compensation of giving a continuous record of umbilical flow. The disturbance caused by the introduction of the flowmeter can be judged by the pressure drop across the flowmeter, tubes and cannulae, which was 10–13 mm Hg at a flow of 400 ml. blood/min. Thus in one experiment femoral arterial pressure rose to its previous level of 58 mm Hg at the end of the preparation. Umbilical venous pressure was initially about 7 mm Hg, rose to a maximum of 55 mm Hg during complete obstruction of placental flow, and fell to 15–17 mm Hg when the flowmeter had been inserted and flow was 400 ml./min. Carotid arterial O_2 saturation fell from 70 to 62%. The rates of umbilical blood flow observed in nine good preparations were about 30% lower on the average than those observed by Cooper, Greenfield & Huggett (1949), using a venous occlusion plethysmograph in lambs of similar maturity.

In four other experiments, venous occlusion plethysmographs were used, of three different sizes according to the size of the foetus. The method of Cooper & Greenfield (1949) was modified in that venous occlusion was effected by direct compression of the *abdominal* umbilical vein, which was exposed and encircled with a tape, instead of by applying pressure to the whole umbilical cord. The rate of decrease of foetal volume was measured with a light float recorder of high natural period. A variable air condenser was mounted on the axis of the float and its movement was detected electronically and displayed on an oscilloscope. The changes were either photographed or recorded on the direct writing instrument. The plethysmographs had Perspex lids; catheters were passed through airtight sleeves for recording blood pressure and injecting drugs into a femoral vein. The rates of umbilical blood flow and of O_2 consumption in the preparation were within the range of those observed previously (Cooper *et al.* 1949; Dawes *et al.* 1954).

Adrenaline hydrochloride, noradrenaline bitartrate and acetylcholine perchlorate were used. Doses are recorded in terms of base.

RESULTS

Injection of adrenaline, noradrenaline and acetylcholine into mature foetal lambs (> 132 days gestation)

Injection of adrenaline into the femoral vein of a mature foetal lamb caused a larger and more immediate increase of heart rate than injection of the same dose into a jugular vein (Fig. 1). The rise of blood pressure was also usually

more abrupt on injection of adrenaline into a femoral vein than on injection into a jugular vein, but the peak increases were much the same. The effect of noradrenaline on the foetal blood pressure and heart rate was very similar to that of adrenaline (Fig. 2). Both compounds caused an increase in umbilical blood flow, commensurate with the increase in blood pressure. For a given increase of blood pressure the increase in umbilical blood flow was rather greater with noradrenaline than with adrenaline (Fig. 2). Similar observations were made in six lambs (Fig. 3). Acetylcholine also caused a greater bradycardia and fall of blood pressure in mature lambs when given by the femoral vein than when given by the jugular vein.

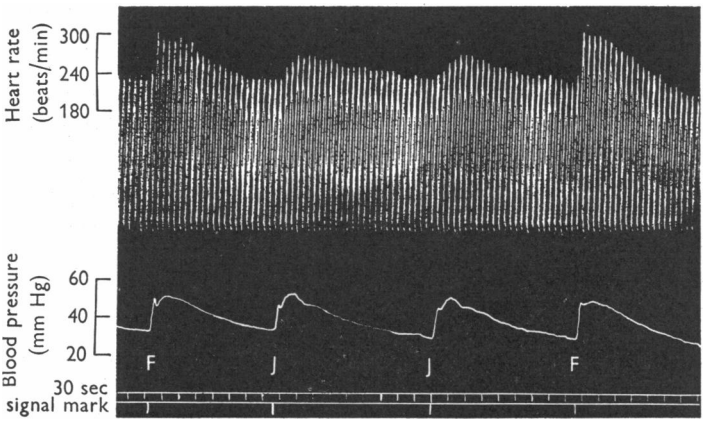

Fig. 1. Lamb 513 A, gestation age 135 days. 10 μg adrenaline caused a larger and more immediate increase of heart rate on injection into a femoral vein (F) than on injection into a jugular vein (J).

When large doses of adrenaline or noradrenaline were injected, the foetal heart rate decreased if the blood pressure rose too high (Fig. 2). After cutting the vagi injection of adrenaline caused only an increase of heart rate. The bradycardia when the vagi were intact was therefore probably due to a depressor reflex, consequent on the rise of blood pressure.

Barcroft (1946) found that, in lambs delivered under spinal anaesthesia, vagotomy caused an increase in heart rate. Reynolds (1954) observed a fall in both blood pressure and heart rate on vagotomy under allobarbitone-urethane. Under pentobarbitone anaesthesia we have usually seen a fall of heart rate and blood pressure in mature lambs. Occasionally there has been no change in heart rate, or as Fig. 2 shows, a fall of blood pressure and an *increase* of heart rate. It is notable that in this experiment the initial blood pressure was unusually high.

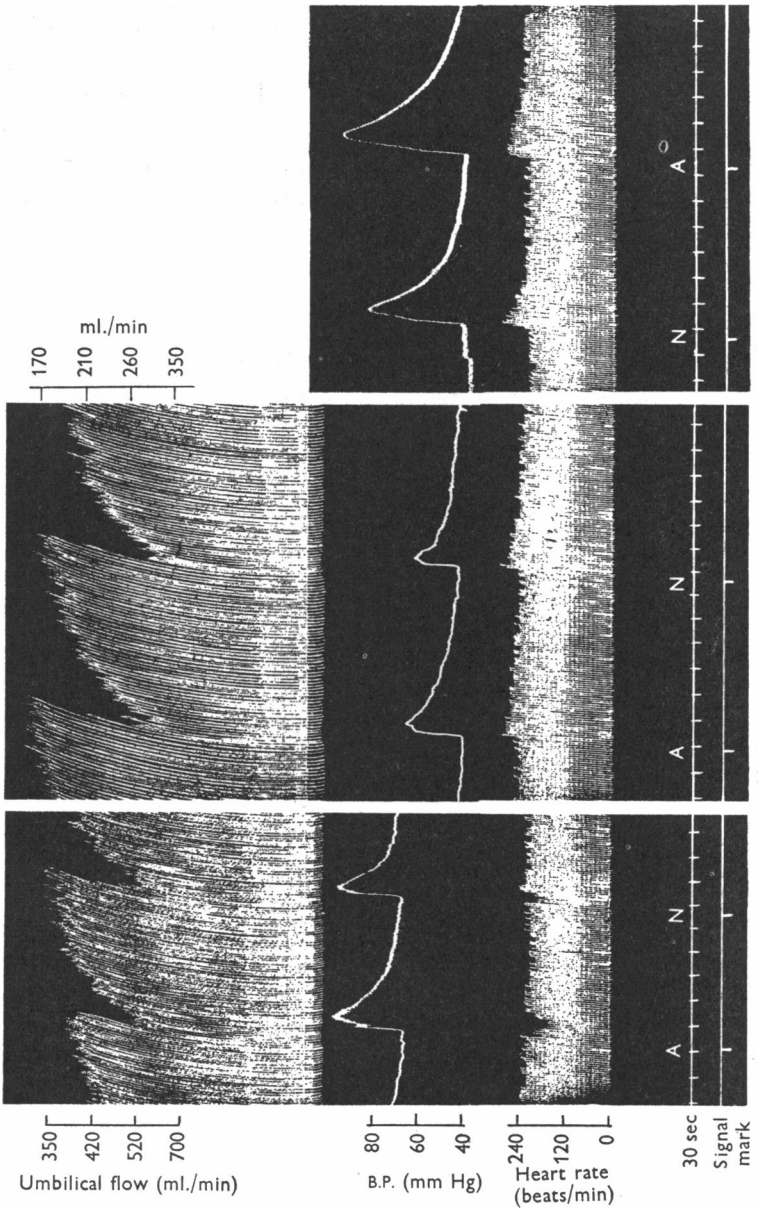

Fig. 2. Lamb 4118, gestation age 135 days. 40 μg adrenaline (A) and noradrenaline (N) were injected into a femoral vein. There was an interval of about 3 min during which both vagi were cut, between the first and second parts of the record. The third part of the record begins within 2 min of tying the umbilical cord and beginning ventilation.

When the umbilical cord was tied and the lungs were ventilated, injection of adrenaline or noradrenaline caused a larger rise of blood pressure than under foetal conditions (Fig. 2). Similar results were seen in six lambs, whether or not the vagi were cut. The change in heart rate after tying the umbilical cord was variable; in some lambs with intact vagi it was clearly complicated by the bradycardia resulting from a large rise of blood pressure.

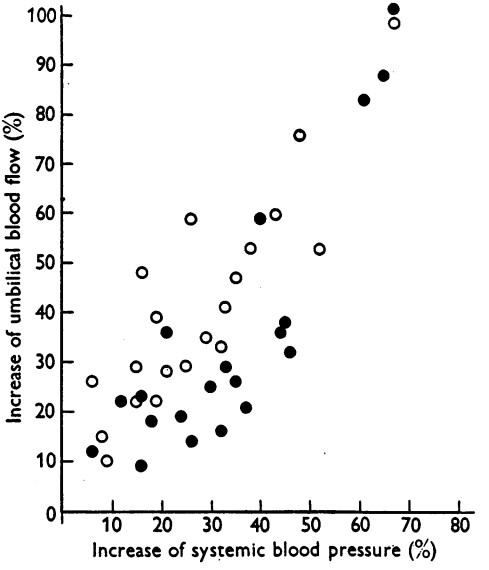

Fig. 3. Data from six mature foetal lambs in which adrenaline (●) or noradrenaline (○) was injected to cause an increase of systemic blood pressure and umbilical blood flow.

Injection of adrenaline and acetylcholine into immature foetal lambs (67–98 days gestation)

The normal gestation period of lambs is approximately 147 days, and the extreme limit of independent viability is reached at about 110 days (Born, Dawes & Mott, 1955). Even in lambs which were younger than this, administration of adrenaline caused a different effect on heart rate according to the route of injection. Fig. 4 shows that the tachycardia produced by 0·125 μg adrenaline in a lamb of 68 days gestation was greater on injection into a femoral than into a jugular vein. In this experiment there was little change in blood pressure. Acetylcholine injected into a femoral vein also had a greater effect on heart rate than on injection into a jugular vein (Fig. 5). The range of effective doses (per kg body weight) of adrenaline and acetylcholine did not appear to differ between mature and immature lambs of 60–140 days gestation.

On injection of adrenaline into mature lambs the increase of heart rate was less for a given increase of blood pressure than in immature lambs. Comparison of Figs. 1, 2 and 4 illustrates this point. In Fig. 6 the percentage increases of blood pressure and heart rate have been related for thirteen lambs arranged in three groups according to their gestation ages. Adrenaline was injected into either a femoral or jugular vein; separate analysis of the results showed the same difference between mature and immature lambs. All results have

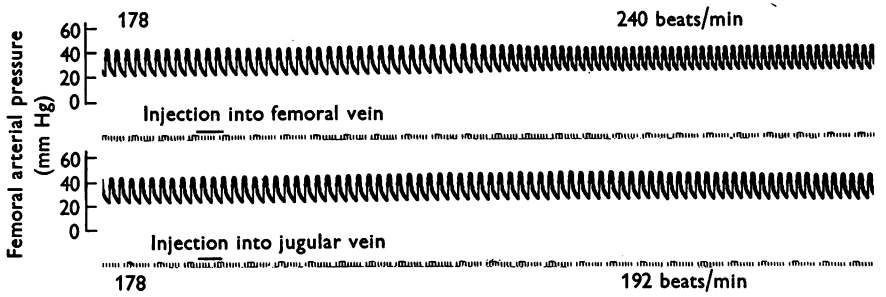

Fig. 4. Lamb 539, gestation age 68 days. A condenser manometer record of femoral blood pressure shows a greater tachycardia on injection of 0·125 μg adrenaline into a femoral vein than into a jugular vein.

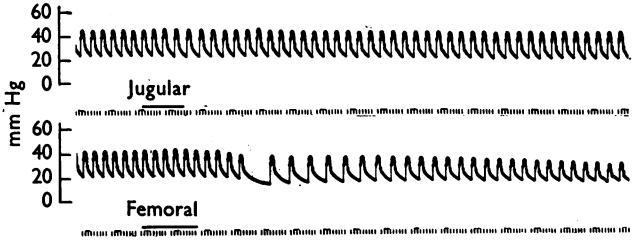

Fig. 5. As Fig. 4. Injection of 20 μg acetylcholine causes a greater bradycardia on injection into a femoral vein (below) than into a jugular vein (above).

therefore been combined in Fig. 6. The relationship shown in this figure may have been due (wholly or in part) to the progressive development of the depressor reflex during the last half of gestation. When a sufficiently large dose of adrenaline was injected into an immature foetus, the blood pressure rose. The youngest lamb in which bradycardia has been seen consequent on this rise of blood pressure was a lamb of 90 days gestation age (Fig. 7). Cutting the vagi abolished this bradycardia. There is good evidence that the heart slows when the vagus is stimulated before this age, but the slowing is not so great as in mature lambs (Barcroft, 1946; Born, Dawes & Mott, 1956).

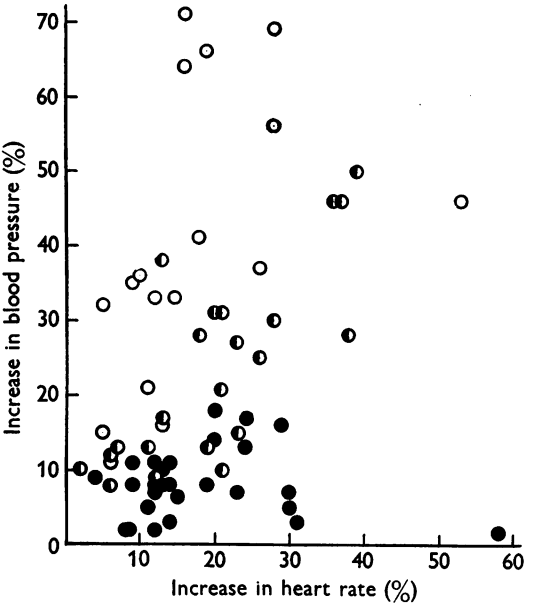

Fig. 6. Data from four lambs of 67–82 days gestation (●), three lambs 89–98 days (◐), and six lambs >130 days (○), showing the relative increases in heart rate and blood pressure on injection of adrenaline.

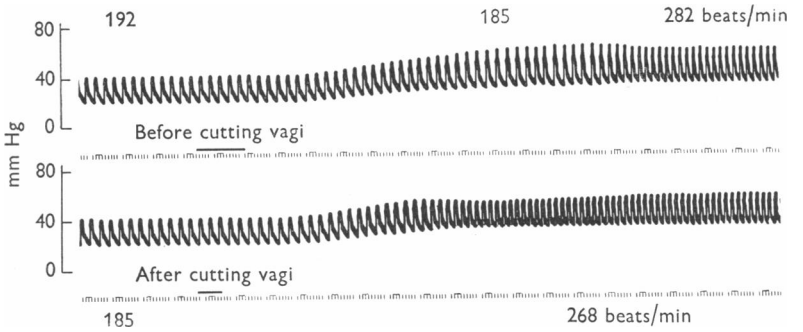

Fig. 7. Lamb 569, gestation age 90 days. A condenser manometer record of femoral arterial pressure shows that the heart slows at first when the blood pressure rises on injection of 2 μg adrenaline by a femoral vein (above). This slowing is abolished by cutting the vagi (below).

DISCUSSION

The observations recorded above confirm the hypothesis that adrenaline, noradrenaline and acetylcholine cause a larger change of heart rate when injected into the femoral vein than the jugular vein of mature foetal lambs. This difference is the more striking because there is good evidence to show that

the volume of blood flow through the inferior vena cava is about four times greater than that through the superior vena cava. A substance injected into the inferior vena cava would therefore be diluted more thoroughly. This evidence also gives additional weight to that view of the foetal circulation which is now supported both by cineangiographic observations (Barclay, Franklin & Prichard, 1944; Barcroft, 1946) and by blood gas analysis (Huggett, 1927; Dawes *et al.* 1954), namely that, although a proportion of inferior vena caval blood passes into the right atrium, none of the superior vena caval blood enters the left atrium through the foramen ovale. It is also interesting to note that sympathetic amines liberated from the adrenal glands (and perhaps also from the organs of Zuckerkandl) would pass to the heart through the inferior vena cava.

The occurrence of the difference in the cardiac response to femoral and jugular injections in foetuses of less than 80 days gestation suggests that the course of the foetal circulation half-way through gestation does not differ fundamentally from that near term. However, the reaction of the circulation to changes imposed upon it does vary with gestation age. As the subsequent paper shows, the increase of blood pressure and heart rate produced by oxygen lack in mature foetal lambs is absent at less than 72 days gestation. It is therefore interesting that injections of adrenaline produce a proportionately larger rise of heart rate for a given rise of blood pressure in young foetuses. This might be due to the progressive development of a depressor reflex from the carotid sinuses and aortic arch during the latter half of gestation (Donatelli, 1940; Ingiulla, 1940). Such an interpretation would not exclude other explanations. For example, Barcroft (1946) showed that the volume of blood in the placenta exceeded that in the foetus up to 100 days; but at birth the quantity of blood in the foetus was 5–6 times that in the placenta. There is no reliable information as to the relative volume of blood flow through foetus and placenta at mid-term. If the distribution of the cardiac output alters during gestation, any differential vasoconstrictor effect of adrenaline on placenta and foetus would change the relation between increase of heart rate and blood pressure.

When small amounts of adrenaline and noradrenaline are injected into foetal lambs there is an increase of umbilical blood flow commensurate with the increase in blood pressure (Fig. 2). This suggests that, at such dose levels, these substances have little influence on the vascular resistance of the umbilical circulation, and should not therefore limit normal placental function. It will be recalled (Dawes *et al.* 1954) that nearly 60% of the combined ventricular output perfuses the placenta of the mature foetal lamb and that any reduction of this flow is probably hazardous for the foetus. The rise of blood pressure which follows administration of adrenaline and noradrenaline may be due to an increase of foetal vascular resistance and to a larger cardiac

output. Further analysis is clearly required before a complete interpretation of the action of pressor amines on the foetal circulation can be offered.

When the umbilical cord is tied and ventilation of the lungs is begun, adrenaline and noradrenaline cause a larger rise of blood pressure than in the foetus. This is probably due in part to the increase in peripheral vascular resistance occasioned by removal of the placenta. There are of course other factors which complicate the issue, such as the change in arterial O_2 saturation at birth, alterations in the degree of dilution to be expected before the injected substance reaches the heart or blood vessels, and the haemodynamic effect of constriction of the ductus arteriosus by sympathetic amines (Born, Dawes, Mott & Rennick, 1956).

SUMMARY

1. Injections of adrenaline, noradrenaline or acetylcholine into foetal lambs caused a larger change of heart rate when given by a femoral vein than by a jugular vein. These observations indicate that, in half term as in full term foetuses, the greater part of the blood reaching the coronary arteries has come from the inferior vena cava through the foramen ovale.

2. Injections of adrenaline and noradrenaline into mature foetal lambs caused an increase in umbilical blood flow commensurate with the increase of blood pressure.

3. Injections of adrenaline and noradrenaline caused a larger rise of blood pressure in mature foetal lambs when the umbilical cord was tied and ventilation was begun, than under foetal conditions.

4. In immature lambs adrenaline caused a greater increase of heart rate for a given rise of blood pressure than in older lambs.

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