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# RELATIONSHIP OF ARTERIAL PRESSURE AND HEART RATE IN FETAL, NEW-BORN AND ADULT SHEEP

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SUMMARY

1. Baroreflex activity was assessed in nine fetal, four new-born and six adult sheep, using the relationship between heart period and arterial pressure. Arterial pressure was raised either by inflating a balloon in the dorsal aorta, by rapid intravenous injection of phenylephrine or methoxamine, or by slow intravenous infusion of methoxamine.

2. In the fetus the three methods gave different estimates of baroreflex sensitivity (balloon, $1{\cdot}3 \pm 0{\cdot}7$ mmHg; injections, $5{\cdot}4 \pm 0{\cdot}5$ msec mmHg; infusions, $7{\cdot}2 \pm 0{\cdot}9$ msec/mmHg) whereas they were comparable in the new-born and adult.

3. Estimates of baroreflex sensitivity were significantly lower in the fetus and new-born than in the adult whichever method was used.

4. In the fetus there were variable changes of heart period when arterial pressure was raised by inflation of the balloon. The responses to injection of phenylephrine or methoxamine were also variable.

5. This variability was not associated with changes in electrocortical activity, the presence or absence of breathing movements or limb movements, or changes of blood gases.

6. In the fetus the heart period frequently did not change unless the arterial pressure was raised by approximately 15 mmHg (to 61 mmHg), suggesting that the threshold for baroreflex activity is above the normal range of arterial pressures before birth.

## INTRODUCTION

It is well established in the fetal lamb that the heart slows when the arterial pressure is raised (Barcroft & Barron, 1945; Dawes, Mott & Rennick, 1956; Biscoe, Purves & Sampson, 1969; Brinkman, Ladner, Weston & Assali, 1969). This has been confirmed in recent studies with unanaesthetized fetal lambs *in utero*, and the fall of heart rate has been attributed to baroreflex mechanisms (Shinebourne, Vapaavouri, Williams, Heymann & Rudolph, 1972; Maloney, Cannata, Dowling, Else & Ritchie, 1977; Ismay, Lumbers & Stevens, 1979). It has often been supposed that the functional maturation of baroreflex pathways is incomplete before birth, but although Shinebourne *et al.* (1972) showed that the sensitivity of the reflex increased with age before and after birth this was not confirmed by Maloney *et al.* (1977). Also, these

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studies with the fetus *in utero* have shown a considerable variation in the heart rate response on different occasions even though the arterial pressure was raised by a similar amount; no explanation has been offered for this variability.

Several methods have been employed to alter arterial pressure in fetal lambs, including intravenous injection of pressor drugs, mechanical obstruction of blood flow in the dorsal aorta by inflating an intra-aortic balloon or extra-aortic cuff, or alteration of fetal blood volume. However they do not give comparable estimates of baroreflex sensitivity. Use of pressor drugs gave estimates of baroreflex sensitivity of approximately 8 msec/mmHg (Maloney *et al.* 1977; Ismay *et al.* 1979) while the use of an aortic balloon or cuff gave values between 1·38 and 3·3 msec/mmHg (Shinebourne *et al.* 1972; Maloney *et al.* 1977). However Faber, Green & Thornburg (1974) estimated the baroreflex sensitivity to be zero when they altered blood pressure by changing the fetal blood volume.

We have therefore examined the relationship between arterial pressure and heart period in the fetal lamb and compared this with the baroreflex responses obtained in the new-born and adult sheep. At each age we have used three different methods to change arterial pressure: inflation of an intravascular balloon in the dorsal aorta, rapid intravenous injection of the $\alpha$-agonist drugs phenylephrine or methoxamine, and slow intravenous infusion of methoxamine. In addition we have attempted to account for the previously observed variability of baroreflex responses in the fetal lambs by assessing baroreflex sensitivity during the different phases of electrocortical activity, during the presence and absence of breathing movements, and during the occasional movements of the fetal lambs.

## METHODS

Observations were made on nine fetal lambs between days 118 and 142 of gestation, on four new-born lambs between 2 and 23 days after birth and on six non-pregnant adult ewes.

The surgical procedures have been described previously (Dawes, Fox, Leduc, Liggins & Richards, 1972). Catheters were implanted into fetuses under halothane anaesthesia into a brachial artery, jugular vein, the trachea and into the amniotic sac at laparotomy at 115–120 days of gestation. Three electrodes were sewn beneath the skin in a line down the sternum to detect the e.c.g. In six fetuses a 5-French balloon catheter (Vygon) was inserted into the dorsal aorta via a femoral artery and positioned so that the balloon was above the renal arteries. In seven fetuses silver electrodes were implanted bilaterally onto the parietal dura to record the electrocorticogram; stainless steel wires were sewn into the inner and outer margins of one eye to record the electro-oculogram. In one fetus small inflatable cuffs were sewn around both carotid arteries; when fully inflated they obstructed blood flow. In another fetus stainless steel wires were sewn into the biceps and triceps muscles of both forelimbs to record the electromyogram associated with limb movement. All catheters and leads were brought out through the ewe's flank. After recovery from anaesthesia the ewes were housed in a metabolic cage, fed a ration of hay and soya meal twice a day, and given free access to water. The ewe and fetus both received penicillin (500,000 units) and streptomycin (0·5 g) on the day of operation and twice a day for 5 days thereafter. The fetal arterial, tracheal, and amniotic catheters were connected to pressure transducers (Devices); the arterial catheter was infused with sterile heparinized saline (500 u./ml.) at 0·2 ml./hr. The true fetal arterial and tracheal pressures were obtained by subtracting amniotic pressure electronically and together with the electrocorticogram, electro-oculogram and heart rate, were displayed on a Schwarzer polygraph at a paper speed of 30 cm/hr. Records were made for 6–24 days.

New-born lambs were housed in a cage with free access to milk. Under halothane anaesthesia catheters were inserted into a jugular vein and brachial artery. Balloon catheters (7-French)

were inserted into the dorsal aorta and inferior vena cava via the femoral artery and vein and positioned so that the balloons lay above the renal vessels. E.c.g. electrodes were attached, and in three of the lambs electrodes were also implanted to detect the electrocorticogram and electro-oculogram and the e.m.g. of the nuchal muscles. Recordings began on the day after operation and continued for 3–4 weeks.

In adult sheep blood pressure was recorded through a 6- or 7-French nylon cannula inserted into one carotid artery through a purse-string suture (under halothane anaesthesia) so that the vessel remained patent. A jugular vein catheter and e.c.g. electrodes were also implanted. Latex rubber balloons, constructed from 5 ml. Foley catheters (Bardick), were inserted into the dorsal aorta and inferior vena cava via the femoral vessels and positioned above the renal vessels.

The arterial pressure was altered either by inflation of the aortic or caval balloon for 5–20 secs, by rapid injection of phenylephrine or methoxamine (25–100 $\mu$g/kg I.V.) or by infusion of methoxamine at 5, 10 and 20 or 10, 20 and 40 $\mu g\ kg^{-1}\ min^{-1}$ for 10–15 min at each dose. The arterial pressure and e.c.g. were displayed on a two-channel recorder (Devices) which was run at 100 mm/sec for the time that the arterial pressure was changed by either inflating the balloon or injecting drugs. This allowed the heart period to be measured from the R–R interval of the e.c.g. to within $\pm 5$ msec, and these values were tabulated against the systolic or mean pressure of each pulse.

In many experiments the heart period and diastolic and systolic pressures were measured (to 0·2 msec and 0·1 mmHg respectively) by a digital sampling system activated from the R wave of the fetal e.c.g. The data were plotted automatically and the regression coefficient calculated using a Nova 1200 computer.

*Baroreflex sensitivity.* Baroreflex sensitivity was estimated as the *slope* of the relationship between arterial pressure and heart period, where the arterial pressure was manipulated over a certain range by the methods described above.

The effect on the arterial pressure and heart period of inflating the balloons was quantified by two methods, as described by Korner, Shaw, West & Oliver (1972):

1. a stimulus–response curve was constructed which related the heart period to the mean arterial pressure for the complete range of initial and final pressures produced by inflating the balloons. For each animal the pressures were grouped into intervals of 10 mmHg and averaged, along with the corresponding heart periods. The average pressure of each 10 mmHg range was obtained by pooling the data for all animals in each group (fetus, new-born and adult) and each mean pressure was plotted against the mean heart period for that pressure range (e.g. Fig. 3*A*). The slope of the relatively straight portion of the S-shaped curve was calculated by least-squares regression for the new-born and adult sheep. In the fetus, where only aortic inflations were performed, the plot was not S-shaped but the initial points of the relatively straight portion of the relationship were used to calculate the slope.

2. The *gain* of the heart period change for each inflation was calculated as:

$$\text{gain} = \frac{\%\text{ change heart period}}{\%\text{ change systolic pressure}}$$

The five beats immediately before the inflation and those at the end were averaged to obtain the values for determining the percentage changes.

For each of the injections of phenylephrine or methoxamine the heart period was plotted against systolic pressure for all the beats from the beginning to the end of the rise in arterial pressure. Where possible (see Results) the slope of the straight portion of each plot was calculated by least-squares regression. When methoxamine was infused, the heart period and arterial pressure were averaged over a 30 secs interval every 5 min starting 15 min before the infusion began and continuing throughout the infusion. These points were plotted and the slope of the relationship determined.

*Thresholds.* Each of the plots of arterial pressure *vs.* heart period was inspected to determine if there was a pressure above which the heart period increased but below which there was no change (e.g. Figs. 1*B* and 4*B*). This particular pressure was designated the *threshold* for the heart period response.

All results are presented as means $\pm$ S.E. of mean.

## RESULTS

*Balloon inflations.* Two hundred and twelve aortic inflations were performed in six fetuses. The inflations were timed to last 5, 10 or 20 sec; examination of fast recorder tracings showed that the arterial pressure was elevated for 5·05 ± 0·15 (S.E. of mean), 9·85 ± 0·14 and 19·5 ± 0·01 sec. Most inflations caused an immediate rise of arterial pressure; the maximum was achieved within two to four beats and maintained until the balloon was deflated. The balloon was sometimes inflated slowly so that the pressure increased gradually throughout the inflation.

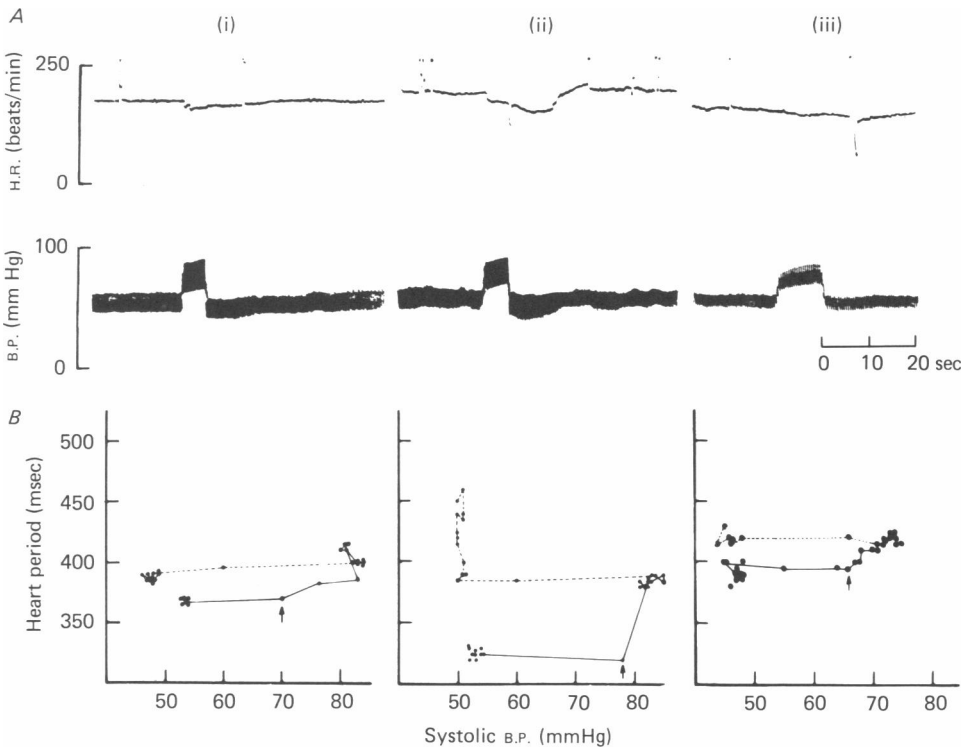


Fig. 1. *A*, three examples (i–iii) on the same day of the heart rate and arterial pressure response to aortic balloon inflation in a fetal lamb of 133 days gestation. H.R., heart rate. B.P., blood pressure. *B*, plot of heart period and systolic pressure for the inflations shown in *A*. Points joined by the continuous line were obtained during the inflation; those joined by the interrupted line were after the inflation. Arrows show the 'threshold' pressure for the heart period response.

The mean rise of fetal systolic arterial pressure was 26 ± 0·48 mmHg (an increase of 52 ± 0·82 %). However, this was associated with a mean increase in heart period of only 33 ± 1·7 msec (9·2 ± 0·47 %). On three occasions the heart period *decreased* during the inflation and on eight occasions the change in heart period was less than 5 msec. Thus despite the relatively large rise in systolic pressure the increase in heart period was small.

Fig. 1 *A* shows the results of three trials where the balloon was inflated for 5–10 sec; Fig. 1 *B* depicts the corresponding plots of heart period against systolic pressure.

These show the variation of the heart period changes that occurred from one inflation to another in the same fetus. Usually the heart period did not increase until the pressure exceeded 60 mmHg. This was true of inflations where the increase of pressure was abrupt (Fig. 1 i and 1 ii), and also where the increase was more gradual and over a longer time (Fig. 1 iii).

Frequently the fetal heart period was changing at the end of the inflation even though the arterial pressure had become steady; it did not return to the pre-inflation values for some time after deflation of the balloon. Occasionally the post-inflation slowing was much larger than that which had occurred during the inflation (Fig. 1 ii).

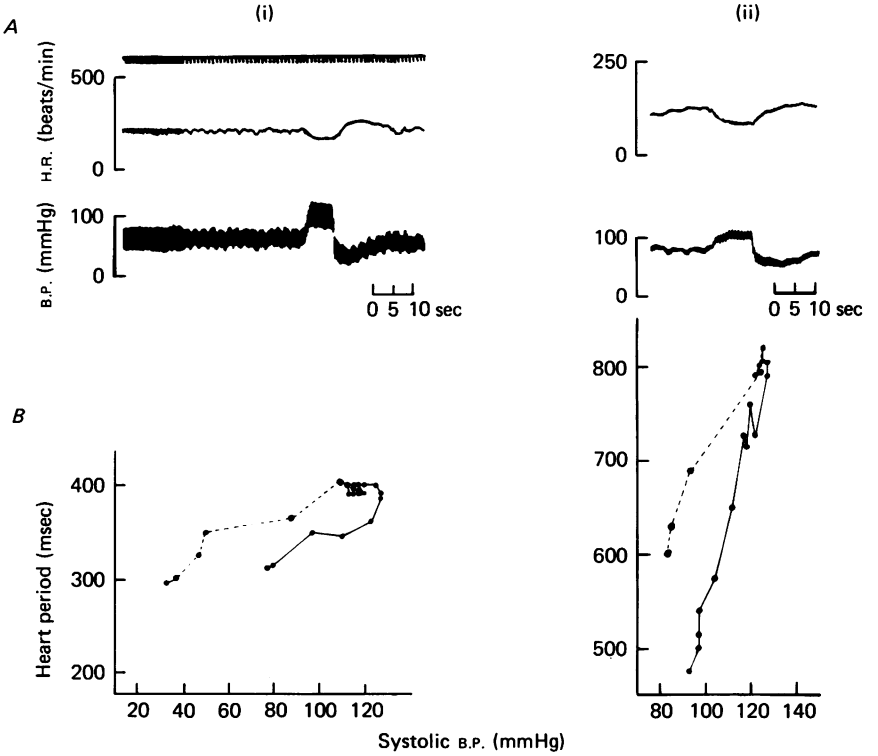


Fig. 2. *A*, examples of the heart rate and arterial pressure response to aortic balloon inflation in an 11-day-old lamb (i) and a ewe (ii). Abbreviations as in Fig. 1. *B*, plot of heart periods and arterial pressures for the balloon inflations shown in *A*.

In contrast, in new-born and adult sheep there was an immediate increase in heart period as the pressure rose. When the pressure had stabilized there were further alterations associated with breathing but otherwise the heart period became steady at the new arterial pressure. The upper part of Fig. 2 shows typical examples of the response to balloon inflation in a new-born lamb and in an adult ewe, with the corresponding plots of arterial pressure and heart period in the lower half of the figure.

The baroreflex sensitivity was expressed both as the *slope* of the curve which related arterial pressure to heart period for the entire range of pressures achieved by all inflations, and also as the *gain* of the response to each balloon inflation (see

Methods). In the new-born and adult the change of heart rate was proportional to the change of pressure; the curve relating heart period to arterial pressure was S-shaped (Fig. 3*A*). The slopes of the central part of these curves were 4·4 ± 1·1 and 10·7 ± 1·1 msec/mmHg for the new-born and adult respectively. These were significantly different (Table 1). Pooling the data from the six fetal lambs where an aortic balloon was used to vary the arterial pressure between 48 and 90 mmHg produced an arterial pressure–heart period relationship with a slope (1·35 ± 0·70 msec/mmHg) not significantly different from zero. Two of the six fetal lambs showed slopes (1·32 ± 0·24 and 1·48 ± 0·6 msec/mmHg) significantly different from zero; the

TABLE 1. Resting mean arterial pressure and heart period, and slope of the arterial pressure–heart period relationship for fetal, new-born and adult sheep when arterial pressure was changed by inflation of an aortic balloon, or intravenous injection or infusion of pressor drugs. Results shown as mean ± S.E. of mean

| | Resting mean arterial pressure (mmHg) | Resting heart period (msec) | Heart period range (msec) | Slope (msec/mmHg) | | |
|---|---|---|---|---|---|---|
| | | | | Balloon | Injection | Infusion |
| Fetus | 44·0 ± 1·8 | 384 ± 3·7 | −420 | 1·3 ± 0·7 (6)* | 5·4 ± 0·5† (4) | 7·2 ± 0·9† (4) |
| New-born | 73·2 ± 8·2 | 333 ± 36·0 | 284–508 | 4·4 ± 1·3‡ (4) | 3·3 (2) | 4·4 (1) |
| Adult | 85·0 ± 4·5 | 558 ± 19·0 | 540–1078 | 10·7 ± 1·1‡ (4) | 28·8 ± 6·0‡ (4) | 12·9 ± 1·9 (4) |

* No. of animals.
† Significantly different from slope obtained from inflation of balloon; $P < 0·05$.
‡ Significantly different from slope obtained from the fetus; $P < 0·05$.

maximum arterial pressures produced by the balloon inflations were higher in these two than in the other fetuses.

The percentage changes of arterial pressure and heart period have been plotted in Fig. 3*B*. The proportion by which arterial pressure was altered was similar for the fetus, new-born and adult.

The gains of the heart period responses in the three groups were compared by taking inflations where the arterial pressure had increased by proportionately the same amount. A range of 40–60 % was chosen because over this range the gain was not related to the amount by which the pressure had changed, and there were sufficient observations in each group. The average gain was least in the fetuses, and the responses were more variable as shown by the higher coefficient of variation (Table 2). The gain was significantly higher for the new-born and adult ($P < 0·001$), and the difference between them was significant ($P < 0·001$). In the fetus the gain was not changed when the arterial pressure was increased 8–10 mmHg by a steady infusion of either 1 μg/min adrenaline (one experiment) or 20 μg/min methoxamine (one experiment), or when the fetus was sedated with 5 mg/kg pentobarbitone given intravenously to the ewe (one experiment). There was no relationship between slope and gestational age (118–142 days).

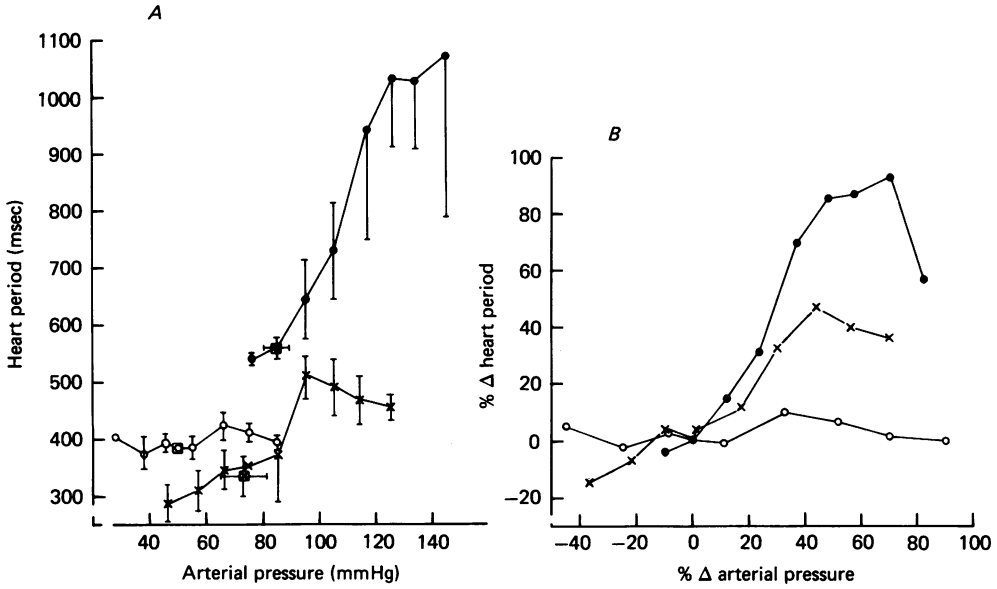


Fig. 3. *A*, the relationship between arterial pressure and heart period for the fetus (○), new-born (×) and adult (●) when the arterial pressure was altered by inflation of aortic and vena caval balloons. Symbols within the squares show the resting value of heart period and arterial pressure. Bars show S.E. of mean. *B*, the percentage changes from the resting level of heart period and arterial pressure derived from the data in *A*.

TABLE 2. Gain of the heart period responses to inflation of an intra-aortic balloon in fetal, new-born and adult sheep where the arterial pressure increased 40–60%

| | Fetus | New-born | Adult |
|---|---|---|---|
| Mean | 0·18 | 0·82† | 1·60‡ |
| S.E. of mean | ± 0·012 | ± 0·046 | ± 0·118 |
| Coefficient of variation | 71·97% | 45·39% | 38·40% |
| Number of inflations (animals) | 131 (6) | 65 (4) | 27 (4) |

† = significantly different from fetus, $P < 0·001$.
‡ = significantly different from fetus and new-born, $P < 0·001$ in each case.

*Drug injections.* Fifty-five injections of 25, 50 or 100 μg/kg phenylephrine were made in four fetuses. The heart period was plotted against the systolic pressure for all pulses from the beginning to the end of the rise in arterial pressure. The plotted relationship was straight for twenty-eight (51%) of the injections, a curved line convex to the pressure axis for nineteen (33%), and in nine (16%) the points were scattered with no simple relationship. These different types of response were observed in the same animal on the same day (Fig. 4).

For each of the twenty-eight straight plots the slope was calculated by least-squares regression. Each heart period was paired with the systolic pressure which belonged to that period; the mean slope was 4·98 ± 0·59 msec/mmHg. Performing the regression by pairing each systolic pressure with the first, second or third subse-

quent heart period did not change either the slope or the correlation between the heart period and arterial pressure consistently.

Most of the curved plots were like that in Fig. 4*B*. The arterial pressure increased by 5–47 mmHg (mean 15·5 ± 2·2 mmHg) above the resting value before the heart period changed. The mean systolic pressure at this point was 61 ± 2·1 mmHg. Thereafter there was a linear relation between heart period and pressure ($r > 0{\cdot}8$) in fourteen of the eighteen examples. The mean slope was 6·18 ± 0·90 msec/mmHg, not significantly different from the slope of the responses which were straight throughout.

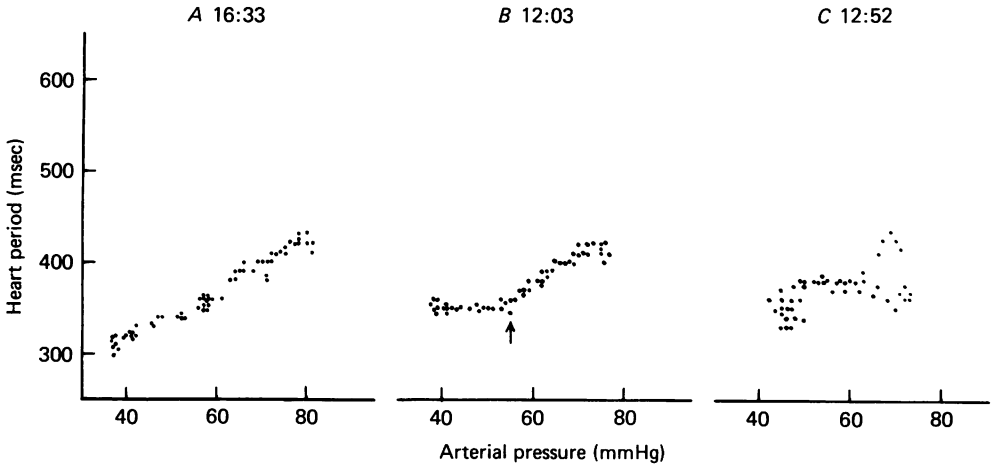


Fig. 4. Variable relation between heart period and arterial pressure when phenylephrine (40 μg/kg I.V.) was injected into a fetal lamb of 125 days gestation. All cardiac cycles from the time of injection to the end of the rise of pressure were plotted. The time of day at which injections were made is shown. In *B* the arrow shows the 'threshold' pressure for the heart period response.

Nine of the injections produced scattered responses (Fig. 4*C*). While some were haphazard, in others the heart rate fell and rose in an uneven manner in the presence of a steady increase in arterial pressure. In contrast to the fetuses, curved or scattered plots were not a feature of the response to injection of the drugs in new-born and adult sheep. Also, the injections caused the arterial pressure to rise more slowly in the fetuses than in the new-born or adults; it was necessary to leave at least 45 min between injections.

Injection of phenylephrine or methoxamine caused significantly steeper responses in the adult sheep than in either the fetus or new-born ($P < 0{\cdot}01$, Table 1). In the fetus and adult (but not in new-born lambs) these slopes were also significantly steeper ($P < 0{\cdot}05$) than the central part of the arterial pressure–heart period relationship when pressure was raised by intravascular balloon inflation.

*Infusions.* Methoxamine was infused intravenously in progressively increasing doses into four fetuses (seven infusions), one new-born lamb (four infusions) and four adult sheep (eleven infusions). Doses of either 5, 10 and 20 μg $kg^{-1}$ $min^{-1}$ or 10, 20 and 40 μg $kg^{-1}$ $min^{-1}$ were infused for 15 min at each dose. In fetuses, new-born and adults alike the arterial pressure increased in a stepwise fashion and was steady,

or almost so, at the end of each 15 min. The heart rate always fell as the pressure rose. The heart period was plotted against the arterial pressure and a straight line was fitted to the data. In the fetus the slope of this relationship was greater than that obtained by balloon inflation or drug injection (Table 1). In new-born and adult sheep the slopes were similar to those obtained by the other methods.

*Thresholds.* Of the 212 aortic inflations performed in the fetuses, inspection of the arterial pressure–heart period plots revealed that a threshold pressure could be discerned in 170 (80 %), and the mean pressure at this point was 62·9 ± 3·5 mmHg. This is not significantly different from the pressure of 61 ± 2·1 mmHg determined

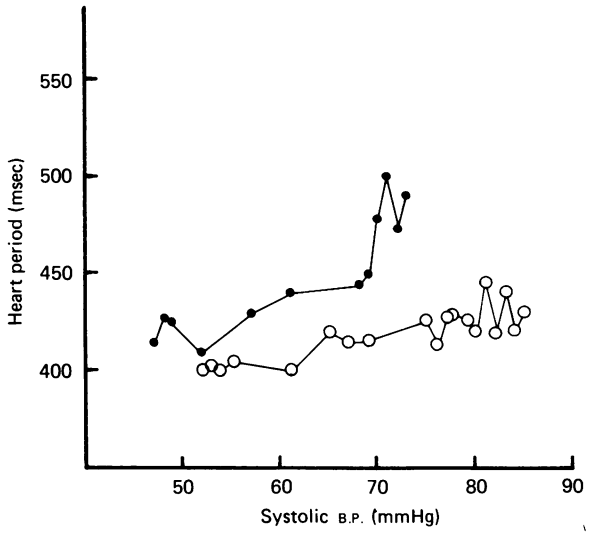


Fig. 5. Relation between heart period and arterial pressure in a fetal lamb of 126 days gestation during high-voltage (○) and low-voltage (●) electrocortical activity. The aortic balloon was inflated three times during low-voltage and five times during high-voltage activities; the data from each electrocortical phase were pooled to produce the plots.

from the nineteen curved plots which followed intravenous injection of phenylephrine. In the adult and new-born both inflation and drug injection produced plots which projected directly through the values for resting heart period and arterial pressure, suggesting that the threshold pressure for the heart period response was at or below the resting arterial pressure. There was no relationship between threshold pressures and gestational age in the fetal lambs.

*Sleep state.* The electrocorticogram and eye movements were recorded in seven fetuses and three lambs. The aortic balloon was inflated when the fetal electrocorticogram showed that either a high or low voltage episode was established. In the new-born low-voltage electrocortical rapid-eye-movement sleep was distinguished from wakefulness by noting the disappearance of e.m.g. activity in the nuchal muscles. The gain of the heart period response to the rise of pressure caused by aortic balloon inflation was calculated.

In each of four fetuses when the aortic balloon was inflated there was a tendency for the gain to be higher during low-voltage rapid-eye-movement sleep, though this

was not statistically significant when the results were averaged. There was a significant difference between high- and low-voltage sleep in two of four fetuses. In one fetus inflations were carried out during several successive high- and low-voltage episodes. The results were combined for each electrocortical phase and the heart period–arterial pressure curves plotted as in Fig. 5. When the systolic pressure exceeded 60 mmHg the increase in heart period was greater during low-voltage activity.

In new-born lambs the average gain of the response to balloon inflation did not change between sleep and wakefulness, although the *lowest* gains observed occurred during low-voltage sleep.

When injection of phenylephrine was used to increase the arterial pressure, there was no difference between the slopes obtained during either high- or low-voltage activity in the fetuses. A $\chi^2$ test showed that the straight, curved and scattered plots did not occur more frequently in either sleep state. It was not possible to test the effect of sleep state on the slope of a response to injection in the lambs because the injection caused them to wake up.

*Fetal breathing and movement.* There was no difference between the gains of responses to aortic balloon inflation (four fetuses) or of the slope of response to drug injection (five fetuses) when these manoeuvres were performed when the fetuses were either breathing or apneic. Inflating the balloon had a number of effects on breathing. After 5–10 sec the breathing movements were sometimes interrupted temporarily or inhibited totally, but more often there was a progressive increase in their amplitude which persisted for several seconds after the balloon was deflated.

In one fetus observed over 48 hr where the e.m.g. of the bicep and tricep muscles was recorded, movement of either one or both forelimbs did not affect the gain of the response to balloon inflation.

## DISCUSSION

The existence of arterial baroreceptor reflexes in the fetus has been considered well established (Barcroft & Barron, 1945; Biscoe *et al.* 1969; Brinkman *et al.* 1969; Shinebourne *et al.* 1972; Maloney *et al.* 1977), although in the two latter papers mention was made of the variation in the degree of slowing of the heart in response to a rise in arterial pressure. The original aim of the present experiments was to examine whether sleep state could exert a general influence on the hind-brain in the fetus and modify the sensitivity of autonomic reflexes such as the baroreflex. However, the most interesting observations were that raising the arterial pressure in the fetus considerably caused only a small increase in heart period, and that the method by which the pressure was raised affected the size of the response. The results suggest that there is a threshold at 60–65 mmHg for the heart period response, so that baroreflex control of heart rate does not operate at resting arterial pressures in a normal fetus *in utero*.

The heart rate responses of fetal and new-born lambs to elevation of arterial pressure by use of an intra-aortic balloon or extra-vascular cuff have been compared previously (Shinebourne *et al.* 1972; Maloney *et al.* 1977). The injection of phenylephrine has been used in fetal, new-born and adult sheep (Ismay *et al.* 1979). A problem with the interpretation of these studies arises from the fact that the complete response curve for heart period and arterial pressure (Korner *et al.* 1972) was not

described. Differences in sensitivity between groups of different ages may result from an alteration of one or several of the parameters which describe this relationship. Although Maloney *et al.* (1977) have described such a curve for fetal and new-born lambs this was calculated from data where the arterial pressure was increased by intravenous injection of phenylephrine, and it is clear from both their study and ours that the injection of phenylephrine and mechanical obstruction of flow in the thoracic aorta do not produce similar estimates of baroreflex sensitivity. Phenylephrine has been shown to alter the mechanical properties of the carotid sinus and to increase the adapted firing rate of afferents from this region (Bergel, Peveler, Robinson & Sleight, 1979). It is therefore unlikely that phenylephrine-induced changes in arterial pressure can be used to determine the stimulus–response relationship as described by Korner *et al.* (1972).

Using vena caval and aortic balloon inflation we have described the relationship between heart period and arterial pressure for the new-born lamb and ewe (Table 1). There is an increase in sensitivity of the reflex and an increase in the range over which the heart periods are changed when the adult is compared with the lamb. It appears that some re-setting of the reflex arc occurs in the new-born period because the rise in arterial pressure from fetal to post-natal life is associated with a decrease, rather than an increase, of the resting heart period.

The stimulus–response relationship was established with less certainty in the fetus for two reasons. First, for each balloon inflation the relationship between heart period and pressure was rarely straight and most of the change in heart period occurred at pressures above 65 mmHg. We did not use linear regression to calculate the slope of the relation as the index of baroreflex sensitivity as was done by Shinebourne *et al.* (1972). Secondly, the fetal heart rate was not steady at the end of the inflation period. Therefore we took the mean of the last five heart periods before deflation.

We did not use a vena caval balloon in the fetuses to lower arterial pressure, and the lower limit of the heart period has not been established. Two pieces of evidence suggest however that it is near to the value of the resting heart period (340–360 msec). Bilateral carotid occlusion in a fetus *in utero* did not cause a reflex rise in arterial pressure and heart period (G. S. Dawes, B. M. Johnston & D. W. Walker, unpublished observations), and Walker, Cannata, Dowling, Ritchie & Maloney (1977) report that arterial hypotension caused by obstructing flow in the vena cava did not result in tachycardia. These observations suggest that the arterial baroreceptors are not loaded at normal fetal arterial pressures, and are consistent with our observation that there appears to be a threshold of 60–65 mmHg for reflex changes of heart period when pressure is raised with an intra-aortic balloon.

These conclusions differ from those of Shinebourne *et al.* (1972) and Maloney *et al.* (1977). Both suggested that baroreflex control of heart rate was present in the fetal lamb, although their estimates of sensitivity are not much greater than ours. Shinebourne *et al.* (1972) found no difference between the fetus and the neonate whereas Maloney *et al.* (1977) found a lower sensitivity in the new-born when compared with the fetus. We have found that, using the balloon to alter arterial pressure, there is a consistent increase of sensitivity and heart period range from the fetus to the adult.

The characteristics of the response to aortic balloon inflation in the fetus, the

variability from trial to trial, the delayed and often considerable slowing after deflation, and also on occasion the lack of response to a large rise in arterial pressure, have not been emphasized before and require explanation. Previous authors have rejected responses where linear regression could not be used to calculate the slope between arterial pressure and heart period (Shinebourne *et al.* 1972), but we consider the irregularity an important feature not seen in the new-born and adult. It is certain that inflation of the aortic balloon in the fetus produces changes in pulmonary arterial pressure and it is possible that it produces changes in atrial and venous pressures which might reflexly activate sympathetic efferent activity and so obscure the vagal effects on the heart. Yet aortic balloon inflation after mid-cervical vagotomy or administration of atropine does not cause tachycardia (Shinebourne *et al.* 1972; Maloney *et al.* 1977). Baroreceptor afferent activity has been recorded from the vagus or carotid sinus nerves of anaesthetized and exteriorized fetal lambs at term (G. S. Dawes, unpublished observations; Biscoe *et al.* 1969; Ponte & Purves, 1973) but it is not clear if the baroreceptors are active *in utero* in the absence of endocrine and other changes induced by operation.

Faber *et al.* (1974) calculated the open-loop gain of the baroreflex of fetal lambs *in utero* to be zero. They altered blood pressure by varying the blood volume and found that arterial and central venous pressures and heart rate increased when the blood volume was increased. Baroreflex mechanisms could not be shown to moderate these changes. The fetal blood volume per unit weight is high (Creasy, Drost, Green & Morris, 1970), and blood volume is an important determinant of fetal blood pressure and placental blood flow (Faber & Green, 1972; Faber *et al.* 1974). Vatner, Boettcher, Hendryx & McRitchie (1975) have shown in the conscious dog that volume loading results in a decrease of baroreflex sensitivity. It is possible, therefore, that the high blood volume is partly responsible for the lower sensitivity of the baroreflex in the fetus.

The influence of chemoreceptors in the fetus is not clear but the delayed effects of balloon inflation on heart rate and breathing are interesting. They could be due to small chemical changes acting on the peripheral or central chemoreceptors. We were unable to measure consistent changes in arterial blood gases and pH after 5 or 10 sec of aortic balloon inflation but it was difficult to obtain rapid samples from long (1·2 m) catheters.

The two other methods of raising arterial pressure (injection or infusion of $\alpha$-agonists) introduced further questions. These three methods produced different estimates of baroreflex sensitivity in the fetus, similar estimates in the new-born, while in the adult the injection method gave an estimate of sensitivity approximately twice that obtained when the balloons or infusions were used. The reasons for the differences are not clear, and the three methods have not been studied under the same experimental conditions before. The arterial pressure was changed by a similar amount when each method was used. With inflation of an aortic balloon the pressure reaches its maximum within 3–6 beats, whereas it rises over 30–90 sec when phenylephrine is injected and over many minutes when the $\alpha$-agonists are infused. The poor dynamic response by the fetus to balloon inflation is seen when Figs. 1 and 2 are compared. It is possible that the baroreceptors in the fetus are able to respond to slow changes of mean arterial pressure but not to rapid and erratic fluctuations about

this level. Alternatively the drugs may have had other actions of slow onset, either centrally or peripherally, which altered the threshold and sensitivity of the baroreflex loop.

Finally, sleep state had only a small influence on the heart rate response to balloon inflation, and no effect on the response to phenylephrine or methoxamine injections. Although Smyth, Sleight & Pickering (1969) showed that baroreflex sensitivity as measured by the injection method was sometimes increased during rapid-eye-movement sleep, this did not account for the variation in baroreflex responses in the fetus. Nor were these effects associated with gestational age, blood gas status, breathing movements, or occasional limb movements.

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