Regional Redistribution of Blood Flow in the Mature Fetal Lamb

By A. G. M. Campbell, G. S. Dawes, A. P. Fishman, and A. I. Hyman

ABSTRACT

Observations on mature fetal lambs delivered under chloralose anesthesia showed that variations in arterial blood gas tensions, caused by ventilation with gas mixtures of differing composition, produced considerable changes in regional systemic blood flows measured with a cannulated electromagnetic flowmeter. Partial asphyxia was associated with a rise in arterial pressure and a reduction in femoral and renal flows; coronary, carotid and superior sagittal venous sinus flows increased owing mainly to coronary and cerebral vasodilatation. Ventilation with air caused an opposite result. The results indicate that a more detailed study of the local and reflex mechanisms controlling vasomotor tone in the mature fetus is necessary.

ADDITIONAL KEY WORDS
carotid flow coronary flow
renal flow asphyxia femoral flow cerebral flow

Previous observations on the circulation in mature fetal lambs have shown that small alterations in blood P\textsubscript{O\textsubscript{2}}, P\textsubscript{CO\textsubscript{2}} or pH are associated with considerable changes in pulmonary vascular resistance, largely by a direct action (1). The umbilical circulation, through which the bulk of the cardiac output passes, is relatively insensitive even to large alterations in blood gas composition (2). Yet comparatively little is known about the regulation of the systemic vascular bed in the mature fetus. The present experiments were intended to fill some of the gaps. No detailed examination of any particular vascular bed has been undertaken, but rather a general study of regional control of systemic vasomotor tone in the mature fetus by variation of the blood gas tensions around the normal fetal values.

Methods

Observations were made on mature fetal lambs (Clun-Hampshire or Masham-Suffolk crossbred) of 138 to 143 days gestation age (term is ~147 days) weighing 2.2 to 6.1 kg. The ewes (and hence the fetuses) were anesthetized with chloralose (30 mg/kg initially iv). The lambs were delivered by cesarean section and were placed on a warmed table alongside the mother, with the umbilical circulation intact. The lambs were covered as much as possible to minimize heat loss. The fetal trachea was cannulated so that the lungs could be ventilated at will, using a Starling Ideal pump. A catheter was passed into a small branch of an external jugular vein so that heparin (10 mg/kg) could be given to the fetus. Regional blood flows were measured with a cannulated electromagnetic flowmeter of high fidelity (of which a full description is given elsewhere [3]); neither baseline nor sensitivity was altered by more than 2% over periods of 5 hr. Repeated calibration is not necessary because we used an absolute instrument; the sensitivity of the gauge head was within 2% of the calculated value. To measure femoral or carotid arterial blood flow, the vessel was divided and rejoined with a short loop of polyvinyl tubing incorporating the flowmeter gauge head and a side tube whence arterial pressure was recorded. To measure superior sagittal venous sinus flow, the skull

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Dr. Fishman was a Fellow of the Commonwealth Fund, on leave from the Department of Medicine, Columbia University College of Physicians and Surgeons, New York.

Dr. Hyman was supported by a Public Health Service Special Fellowship 1-P3-GM-53, 038-01 from the National Institutes of Health, on leave from the Department of Anesthesiology, Columbia University College of Physicians and Surgeons, New York.

Accepted for publication July 1, 1967.
TABLE 1

Measurements of Arterial Blood Gas Tensions, Mean Arterial Pressure and Blood Flow in Mature Fetal Lambs

<table>
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<tr>
<th>Lamb no.</th>
<th>Gestation age (days)</th>
<th>PO2 (mm Hg)</th>
<th>PCO2 (mm Hg)</th>
<th>Arterial pressure (mm Hg)</th>
<th>Flow per min (ml/kg per min)</th>
<th>PO2 (mm Hg)</th>
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(A) Before ventilation (B) Ventilation with 3% O2 and 7% CO2

*Simultaneous measurements of femoral and carotid flows in the same lambs. A and B indicate the first and second delivered twin, respectively.

was opened in the midline and a fine silk thread was passed around the sinus. This was then cannulated and attached via the flowmeter gauge head to a polyvinyl catheter already placed in an external jugular vein. Left circumflex coronary arterial flow was measured from a flowmeter in a loop between the left carotid and the peripheral end of the left circumflex artery, exposed in the left atrioventricular groove. Left renal flow was measured either in a loop between the renal and axillary veins, or in one between a femoral and renal artery. Injection of 1 ng bradykinin (Sandoz) into either the femoral or carotid arteries caused a large vasodilatation, so it is evident that as much care must be taken with systemic vascular beds as with the pulmonary circulation of the fetal lamb, to prevent the formation of kinins from contact between blood and glass or foreign surfaces other than plastic.

Arterial and venous pressures were measured with Elema inductance manometers and were recorded on a Schwarzer polygraph. Heart rate was recorded from a pressure pulse or the electrocardiogram using a rapid response rate-meter (4) on the Schwarzer polygraph. Mean arterial pressures and flows were also plotted on an X-Y recorder to give a visual indication of the pressure-flow relationship.

Blood samples (0.6 to 0.8 ml) were taken from a carotid artery (either from an external loop or from a fine catheter introduced through a thyroid branch). They were analyzed at once for PO2 and PCO2 with electrodes using a Beckman 160 gas analyzer. The electrodes were calibrated with gas mixtures of known composition. The observations were corrected when necessary for the difference between electrode and fetal temperature, measured from the esophagus.

Results

Table 1, section A, shows the range of initial observations before ventilation of the lungs. Ventilation of the lungs was begun with 3% O2 and 7% CO2 in N2, using a respiration pump-stroke (about 50 to 70 ml in a 3- to 4-kg lamb) sufficient to give a peak
intratracheal pressure of 30 to 35 mm Hg (5) initially. This causes no significant change in arterial Po₂ or Pco₂ (6, 7) (Table 1, section B). The effect on heart rate was variable, sometimes a small fall (as in Fig. 1) but often no significant change. There was always a fall in arterial pressure of 5 to 7 mm Hg (Fig. 1), but this was rarely sustained for more than a few minutes. The measurements recorded in Table 1, section B, were taken after these transient variations had subsided. Mean venous pressure in the superior vena cava rose by 1 to 2 mm Hg. The immediate effect on coronary and sagittal venous sinus effluent was to cause a small reduction in flow which was approximately proportionate to the reduction in arteriovenous pressure gradient. In the femoral, carotid and renal vascular beds, there was either a slight reduction in flow, no obvious change, or a trifling increase (Fig. 1).

Circulation Research, Vol. XXI, August 1967

When the gas mixture used to ventilate the lungs was changed from 3% O₂ and 7% CO₂
Ventilation with 1% O₂

**FIGURE 2**

*Mature fetal lamb (A) before and (B) after beginning ventilation. On changing the gas used for ventilation from 3% O₂ and 7% CO₂ in N₂ to air there was a rise in femoral and a fall in carotid blood flow, which were reversed on returning to the original gas mixture.*

In N₂ to air, fetal arterial Po₂ rose and Pco₂ fell (compare Table 1, sections B and C). The wide variations in these changes in individual lambs has been observed before (6, 7) and was attributed to variations in umbilical blood flow, which continues after ventilation is begun. As before, there was a small fall in heart rate, and occasionally in arterial pressure, with no significant change in venous pressure. In each lamb in which it was measured, femoral and renal flow increased, while coronary arterial, carotid and sagittal venous sinus effluent decreased. Figure 2 illustrates the immediate fall in carotid flow and rise in femoral flow on ventilation with air. In every lamb the changes were reversed on returning to ventilation with 3% O₂ and 7% CO₂ in N₂, as also shown in Figure 2. This illustration was chosen because it is an average record in which the effect of varying the ventilating gas mixture is superimposed on a changing vascular tone, more obvious in the femoral than the carotid vascular beds, but present in both. Such slow variations, upwards or downwards, are not uncommonly present in the fetal lamb under light chloralose anesthesia.

Asphyxia was caused either by occlusion of the umbilical cord in the absence of pulmonary ventilation (Fig. 3), or by stopping the respiration pump after tying the cord or by varying the gas mixtures used for ventilation (Fig. 4). In the first instance, arterial Po₂ falls to 10 mm Hg or less within 2 min (8), there is a rapid rise of arterial pressure and an abrupt fall of heart rate to ~ 100 beat/min (Fig. 3). In the other two instances...
there is a residuum of O\textsubscript{2} within the pulmonary airways, the arterial P\textsubscript{O}\textsubscript{2} falls more gradually and there is a much less rapid change in arterial pressure. Central venous pressure rises by 5 to 8 mm Hg. The heart rate may accelerate initially and only begins to fall slowly after several minutes. The results were qualitatively the same whether asphyxia was induced rapidly or slowly. During asphyxia femoral and renal flows decreased, while carotid, cerebral and coronary flows increased. The values given in Table 1, section D, are those observed after a period of asphyxia of slow onset, of 4 to 8-min duration, during which there had been a rise of arterial pressure and a small decline in heart rate from the initial value during ventilation with room air (range 180 to 250 beat/min).

In some instances (as in Fig. 4) the arterio-venous pressure difference across the brain was actually reduced when cerebral flow had greatly increased, and there was then no doubt that the increase in flow was due to vasodilatation; this was observed in each of the 3 lambs in which sagittal venous sinus effluent was measured. Similarly, in each of the 4 lambs in which coronary flow was measured, asphyxia was on one or more occasions prolonged until the arterial pressure had fallen to its initial value; at this time flow was still more than threefold that at the onset of asphyxia. Once again this constitutes clear evidence of active vasodilatation. In the femoral and renal vascular beds no difficulty in interpretation arose, since flow always fell rapidly soon after arterial pressure began to rise, indicating vasoconstriction.

A period of ischemia in these vascular beds was always followed by reactive hyperemia. When blood flow through the femoral, renal, coronary or sagittal venous sinus vascular beds was briefly arrested (e.g. as during cannulation) and was then released, blood flow rose to a maximum and then declined to a much lower plateau. But when a single carotid artery was occluded, flow through the other carotid nearly doubled; and when the occluded vessel was released blood flow through it returned rapidly to its previous level and did not overshoot. This is attributed to the large arterial anastomoses between the
branches of the carotid arteries which prevented ischemia of the vascular bed when one vessel alone was occluded.

Discussion

The blood flow (Table 1) observed in the femoral, carotid, renal and coronary vascular beds in the mature fetal lamb, delivered from the uterus under chloralose anesthesia but with an intact umbilical cord, seems to constitute a comparatively small fraction of the combined output of both ventricles. Umbilical blood flow averaged 170 ml/kg per min in this type of preparation (9), and the mean combined output of both ventricles exceeded 300 ml/kg per min (10) (Dawes, Groom, Mott, Rowlands and Thomas, unpublished observations). The relatively small blood flows are not due to mechanical factors, because the resistance to flow of the extracorporeal part of the flow circuits was negligible, < 3 mm Hg at the maximum flows observed. Moreover, flow more than quadrupled in the femoral artery on injection of bradykinin, and in the coronary and cerebral circuits during asphyxia. It is also evident that the low flows cannot be attributed to highly abnormal blood gas tensions. The values observed and shown in Table 1 are not dissimilar to those recorded elsewhere under different experimental conditions (e.g. in the absence of general anesthesia or in utero). But more persuasive still is the internal evidence. The results show that when the mature fetal lamb becomes asphyxiated there is vasodilatation in the coronary and cerebral vessels. It is also evident that the low flows cannot be attributed to highly abnormal blood gas tensions. The values observed and shown in Table 1 are not dissimilar to those recorded elsewhere under different experimental conditions (e.g. in the absence of general anesthesia or in utero). But more persuasive still is the internal evidence. The results show that when the mature fetal lamb becomes asphyxiated there is dilatation in the coronary and cerebral vessels. The fact that flow appears relatively low in these vascular beds in the normal lambs of these experiments (Table 1, section A) suggests that we must look elsewhere for an explanation. There are possibilities. Blood flow through these circuits should be low under general anesthesia, when muscular tone is abolished and oxygen consumption reduced. Also, chloralose anesthesia is well known among physiologists to give a preparation in adult animals with a relatively high vascular resistance.

These considerations are peripheral to the main subject of the investigation, which was to conduct a preliminary survey of some of the principal systemic vascular beds of a mature fetal animal to determine whether they were sensitive to changes in blood gas tensions about the normal fetal values. The results clearly demonstrate that they are. A rise in Po₂ and fall in Pco₂ is associated with a rise in renal and femoral flows, and a fall in carotid, coronary and cerebral flows. Partial asphyxia of the fetus has the opposite effect.

There are three principal methods by which such changes in regional vascular tone may be effected—by local mechanisms as in adult animals, by reflex mechanisms (which are of predominant importance in skin and skeletal muscle), and by liberation of agents such as norepinephrine or angiotensin into the circulation. No deliberate attempt was made in the present experiments to distinguish between these possibilities or to differentiate between the effects of Pco₂ or pH changes in the blood and tissues. But one or two incidental observations are worth brief discussion. For instance, the femoral vasoconstriction observed during acute asphyxia (Fig. 3) clearly begins too soon, within 10 secs of cord occlusion, to be explained other than by a reflex means. Subsequent unpublished observations have confirmed this conclusion. The direct effect of ischemia in the femoral circulation is to cause reactive hyperemia. General asphyxia and local ischemia both cause vasodilatation in the heart and brain, so the question of reflex control is more difficult to assess. The well authenticated tolerance of an immature fetus to hypoxia could be associated with a sensitivity of the local mechanisms which regulate blood flow which is different from that in the adult. The sensitivity and sites of the control mechanisms may be different, but the results suggest that there are mechanisms, local or reflex (probably both), which regulate the systemic circulation in a mature lamb actively, in a manner analogous to that which is normally operative in adults.

It is also evident, as has long been suspected, that during fetal asphyxia there is a
redistribution of cardiac output, not only by vasoconstriction in the pulmonary, renal and femoral vascular beds but by vasodilatation in the coronary and cerebral vessels. The umbilical circulation (through the fetal side of the placenta) is comparatively unreactive (2). In these experiments no attempt has been made to distinguish blood flow to skin, skeletal muscle and bone within the hindlimbs. But it is worth mentioning that in younger fetal lambs (at say, 110 to 120 days gestation age or 0.75 to 0.82 of term), asphyxia causes rapid blanching of the semitransparent skin and underlying skeletal muscle.

Acknowledgment
We thank the Medical Research Council for apparatus used in this investigation, and Mr. A. Ryder for technical assistance.

References
such a displacement should be considered as a regurgitation in the sense that the term has come to assume, depends, of course, on whether the door frame or the door itself is considered as the line of division between the room and the corridor. In any case, no considerable volume could be displaced auricle-ward, but such a displacement as occurs must cause some elevation of auricular pressure. Are there any indications on the pressure curve that this takes place? Even a casual inspection of the pressure curves such as are shown in figures 1 and 2, indicates that the intra-auricular pressure rises synchronously with or very slightly after the first elevation of intraventricular pressure. These and similar elevations shown also in the published curves of Piper (5), as well as in those of Garten and Weber (18), might readily be accounted for by such a regurgitation. Close inspection of the intraventricular pressure curves also indicates that the pressure increases in two stages, first slowly, t-n, then suddenly changing to a steeper

Fig. 2. Synchronous records of aortic left auricular and left ventricular pressures. Letters same as in figure 1.
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Circ Res. 1967;21:229-236
doi: 10.1161/01.RES.21.2.229

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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