CONTROL OF THE FOETAL CIRCULATION

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SUMMARY

Foetal cardiac output is high, and the heart has not been shown to have the sustained reserves demonstrated in the adult heart. About 40% (~ 200 ml kg body weight⁻¹ min⁻¹) of the combined output of both ventricles (CVO) in unanaesthetized foetal lambs in late gestation is directed to the umbilical circulation. At least one-half of the systemic flow (~ 300 ml kg body weight⁻¹ min⁻¹) goes to skin and carcass. About 50% of the remainder (10% CVO) is shared by brain, heart and kidney and the rest by other viscera; less than 6% CVO perfuses the lungs. Hypoxaemia, acidaemia and various vasomotor agents influence the partition of cardiac output between systemic and umbilical circulations, with or without relatively small changes of blood pressure, which is low by adult standards. In general, the conductance of systemic circuits is more susceptible to change than that of the umbilical. Both cerebral and myocardial blood flow increase several-fold during hypoxaemia. The additional volume flow of blood demanded by such vasodilatation in organs forming a relatively small proportion of body weight is more than accounted for by concurrent vasoconstriction in muscle (which contributes a substantial fraction of body weight) and other tissues. Both humoral and reflex neural mechanisms are involved in these adjustments.

INTRODUCTION

The foetal circulation works under conditions very different from those found in adult mammals. Arterial pressure is low (see Table 3) and similar in all circuits and systemic arterial blood gas tensions are asphyxial by adult standards; average values reported for control foetal lambs (Tables 1 and 3) were $P_a.O_2$ 20–24 mmHg and $P_a.CO_2$ 40–48 mmHg while pH was 7.31–7.39.

Quantitative information about the foetal circulation has been acquired almost entirely from the foetal lamb in the last one-third of gestation (full term ~ 147 days). Unlike the adult, the foetal cardiac ventricles pump in parallel and their combined output (CVO) is about 0.5 l kg body weight⁻¹ min⁻¹. About 60% of this goes to the oxygen-consuming circuits of the foetal body and 40% to the umbilical circulation (Table 1).

Table 2 lists the effects on cardiac output of various stimuli. The responses were for most procedures relatively small and the foetal heart does not seem to have a great deal of reserve.

The changes of conductance in systemic and umbilical circuits do not necessarily parallel one another following the application of any particular stimulus. A change of arterial pressure (Table 3) may or may not accompany a change of gross distribution.
Table 1. Partition of combined output of both ventricles (CVO) between umbilical and systemic circulation. Mean control values from 9 investigations on unanaesthetized foetal lambs

<table>
<thead>
<tr>
<th>Gestation age (days)</th>
<th>Umbilical</th>
<th>Systemic</th>
<th>Umbilical flow as % CVO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ml kg body weight^-1 min^-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100-147</td>
<td>264</td>
<td>340</td>
<td>43</td>
</tr>
<tr>
<td>Toubas et al. (1981)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>122-142</td>
<td>191</td>
<td>273</td>
<td>41</td>
</tr>
<tr>
<td>Cohn et al. (1974)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>125-135</td>
<td>195</td>
<td>302</td>
<td>39</td>
</tr>
<tr>
<td>Lorijn &amp; Longo (1980)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>123-140</td>
<td>177</td>
<td>361</td>
<td>33</td>
</tr>
<tr>
<td>Iwamoto et al. (1979)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>125-135</td>
<td>190</td>
<td>284</td>
<td>40</td>
</tr>
<tr>
<td>Lorijn et al. (1980)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120-131</td>
<td>191</td>
<td>363</td>
<td>34</td>
</tr>
<tr>
<td>Iwamoto &amp; Rudolph (1981)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>115-133</td>
<td>210</td>
<td>316</td>
<td>40</td>
</tr>
<tr>
<td>Iwamoto &amp; Rudolph (1979)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>139</td>
<td>158</td>
<td>248</td>
<td>39</td>
</tr>
<tr>
<td>Creasy et al. (1973)</td>
<td>202±11</td>
<td>310±13</td>
<td>Mean 39±2</td>
</tr>
</tbody>
</table>

Table 2. Percentage change from control values of cardiac output (CVO) in foetal lambs subjected to various stimuli

<table>
<thead>
<tr>
<th>Decrease (% )</th>
<th>Increase (% )</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Blood volume +10%</td>
<td>11</td>
</tr>
<tr>
<td>-10%</td>
<td>27</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>5</td>
</tr>
<tr>
<td>Hypoxaemia</td>
<td>23</td>
</tr>
<tr>
<td>Acidaemia</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>13</td>
</tr>
<tr>
<td>Tri-iodothyronine</td>
<td>22</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>17</td>
</tr>
<tr>
<td>Saralasin</td>
<td>1</td>
</tr>
<tr>
<td>Placental embolization</td>
<td>9</td>
</tr>
<tr>
<td>†Uterine ischaemia -50%</td>
<td>40</td>
</tr>
<tr>
<td>-75%</td>
<td>40</td>
</tr>
</tbody>
</table>

References as in Tables 1 and 3 with the addition of
* Gilbert (1980)
† Yaffe et al. (1982)

of cardiac output. In any system of parallel circuits any change in one circuit will, other things being equal, affect all other circuits. In general, the conductance of the umbilical circulation seems somewhat less susceptible to alteration than that of the systemic circulation. Hypoxaemia, acidaemia, noradrenaline and vasopressin cause larger reductions of systemic than of umbilical flow but raised plasma (T₃), angiotensin II and saralasin (sar-i, ala-8 angiotensin II; a competitive inhibitor of angiotensin II) increase systemic more than umbilical conductance (Table 3).
Table 3. Vascular conductance (ml·kg body weight$^{-1}$·mmHg arterial pressure$^{-1}$) of umbilical and systemic circulations in foetal lambs

<table>
<thead>
<tr>
<th>Gestation age (days)</th>
<th>Condition</th>
<th>Umbilical</th>
<th>Systemic</th>
<th>Total</th>
<th>Δ Conductance (%)</th>
<th>Mean arterial pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100–147</td>
<td>Control</td>
<td>5.18</td>
<td>6.67</td>
<td>11.85</td>
<td>-20</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Haemorrhage</td>
<td>4.15</td>
<td>5.48</td>
<td>9.63</td>
<td>-18</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>3.35</td>
<td>4.79</td>
<td>8.14</td>
<td></td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Hypoxaemia</td>
<td>3.28</td>
<td>3.52</td>
<td>6.8</td>
<td>2</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>3.10</td>
<td>4.79</td>
<td>7.89</td>
<td>-13</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Acidaemia</td>
<td>2.70</td>
<td>2.30</td>
<td>5.0</td>
<td>-52</td>
<td>76</td>
</tr>
<tr>
<td>122–142</td>
<td>Control</td>
<td>3.93</td>
<td>8.02</td>
<td>11.95</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Noradrenaline</td>
<td>3.90</td>
<td>5.83</td>
<td>9.28</td>
<td>-1</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>4.04</td>
<td>6.04</td>
<td>10.08</td>
<td>-33</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Vasopressin</td>
<td>3.59</td>
<td>3.73</td>
<td>7.32</td>
<td>-11</td>
<td>56</td>
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<tr>
<td></td>
<td>Control</td>
<td>4.06</td>
<td>7.72</td>
<td>11.78</td>
<td>-38</td>
<td>47</td>
</tr>
<tr>
<td>125–135</td>
<td>Tri-iodothyronine</td>
<td>4.53</td>
<td>9.98</td>
<td>14.51</td>
<td>+11.6</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>4.57</td>
<td>6.87</td>
<td>11.44</td>
<td>+29.3</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Angiotensin II</td>
<td>3.73</td>
<td>7.27</td>
<td>11.0</td>
<td>-18</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>5.09</td>
<td>6.42</td>
<td>11.51</td>
<td>+6</td>
<td>47</td>
</tr>
<tr>
<td>120–131</td>
<td>Saralasin</td>
<td>4.82</td>
<td>8.29</td>
<td>13.11</td>
<td>-5</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Placental embolization</td>
<td>-31</td>
<td>2</td>
<td>-33</td>
<td></td>
<td>41</td>
</tr>
</tbody>
</table>

* Pressures similar in control and experimental animals.
Umbilical circulation

Under control conditions in the unanaesthetized foetal lamb, the umbilical vessels which are widely patent in utero transport blood at ~ 200 ml kg\(^{-1}\) min\(^{-1}\) at an arterial pressure of 40–50 mmHg (Tables 1 and 3).

Placenta and foetal membranes

Some 27% of the foetal blood has been estimated to be within the umbilical circulation in goats (Novy & Metcalfe, 1970). When the blood volume of foetal lambs was either reduced or increased (Faber et al. 1973), flow in the infra-renal abdominal aorta changed in the same direction according to the equation

\[
\text{flow } \% = -70.8 + 1.71 \times \text{volume } \%
\]

Although both femoral arteries were tied in this preparation, 16% of the flow measured by the electromagnetic flowmeter was shown by microsphere injections to be extra-placental. The fraction of umbilical blood flow perfusing the intercotyledonary chorion found in sheep and goats, estimated from the distribution of radioactive microspheres, is ~ 6.2 ± 0.8% (Makowski et al. 1968). This shunt is large enough to be of importance in relation to the maternal–foetal oxygen gradient (Campbell et al. 1966).

Umbilical vascular conductance is little affected by hypoxaemia (as in exteriorized preparations; Dawes, 1968) or by infusions of noradrenaline. It is reduced by haemorrhage as might be expected from equation 1, and by acidaemia, vasopressin and angiotensin II. The only situation in which increased conductance has been observed was in lambs receiving T₃ (Table 3). These had a high cardiac output (Table 2) but arterial pressure was in the normal range. Blood volume was not measured but packed cell volume was in the normal range.

In the unanaesthetized foetus the umbilical fraction of cardiac output was significantly raised in hypoxaemia in chronically catheterized foetal lambs (Cohn et al. 1974; Sheldon et al. 1979). Much of the increase may result from accompanying rises of arterial pressure which in turn have been attributed to increased levels of circulating catecholamines (Jones & Robinson, 1975). Infusion of noradrenaline (1 μg kg\(^{-1}\) min\(^{-1}\)) (Lorijn & Longo, 1980) and of vasopressin (6.8–36.4 μU ml\(^{-1}\)) (Iwamoto et al. 1979) have been shown to increase the proportion of cardiac output perfusing the umbilical circuit. A small decrease in umbilical vascular resistance has been found at excessively high \(P_{a,CO_2}\) (> 80 mmHg (Walker et al. 1976)).

Umbilical blood flow increases with gestational age and the driving pressure required for any given flow tends to increase. Reduction of pressure by aortic constriction in exteriorized lambs (Dawes, 1968) or by haemorrhage in chronically catheterized lambs (Toubas et al. 1981), reduced umbilical flow. There was little effect of changes in blood gas tensions on the umbilical vascular bed in such experiments (Dawes, 1968). In unanaesthetized foetal lambs placental blood flow was not systematically related to \(O_2\) content (Peeters et al. 1979). The balance of evidence suggests that placental circulation does not act as a collapsible circuit in which the
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surrounding tissue pressure is determined by the uterine circulation. It has been proposed (Faber & Green, 1972; Longo & Power, 1973) that umbilical blood flow is regulated by change of cardiac output caused by variation in the transplacental flow of water and electrolytes. The theoretical basis for these propositions assumes that the foetal placental capillary follows Starling's Law, and that small changes of foetal systemic arterial pressure are transmitted to the capillaries of the exchanging area. Thus if arterial pressure falls, with a resulting decrease of umbilical blood flow, the fall of capillary pressure on the foetal side of the placenta would favour an increased flow of water and electrolytes from mother to foetus, resulting in an increased foetal blood volume. This would then lead to an increased venous pressure and increase of cardiac output, restoring arterial pressure and umbilical blood flow. While much of this proposal remains theoretical the appropriate relationship has been demonstrated (Faber et al. 1973) between blood volume and placental blood flow in chronically catheterized foetal lambs.

Lack of complete pressure-flow curves in whole animal preparations requires that concurrent observations of instantaneous changes of umbilical pressure and flow be assessed in relation to any other accompanying cardiovascular changes. Isoproterenol, dopamine, histamine and tolazoline do not change umbilical flow or resistance. Adrenaline, noradrenaline and acetylcholine do not change calculated umbilical vascular resistance but are accompanied by alterations of blood pressure and/or foetal heart rate. However, doses in the \( \mu g \) range of angiotensin II, 5-hydroxytryptamine, bradykinin and prostaglandins \( E_1, E_2 \) and \( F_2 \) reduce umbilical blood flow and increase calculated vascular resistance (Berman et al. 1978). Membrane flow as well as placental was substantially reduced following \( PGE_2 \) injection.

The umbilical circulation is unusual in that neither bradykinin nor \( E \) series prosta-
glandins are vasodilatory. The reduction of umbilical flow following infusion of saralasin is the consequence of an increase in foetal vascular conductance and a small fall of umbilical conductance.

Regional circulations

Cerebral circulation

Simultaneous measurement of carotid blood flow with an electromagnetic flow transducer and by microspheres showed that in the mature foetal lamb at normal blood gas tensions, 42–87% of the carotid blood flow was distributed to extra-cerebral structures (Dunnihoo & Quilligan, 1973). Distribution of cerebral blood flow is not uniform (Ashwal et al. 1980; Johnson et al. 1979; Palahniuk et al. 1980); as measured by the microsphere method the deeper structures receive up to double the blood flow per unit volume of the cortex. The average cerebral flow in foetal lambs at normal oxygen tensions is high (100–200 ml.100 g\(^{-1}\).min\(^{-1}\)), compared with those accepted for adult humans (53 ml.100 g\(^{-1}\).min\(^{-1}\)) and goats (45 ml.100 g\(^{-1}\).min\(^{-1}\)) (Dunnihoo & Quilligan, 1973). Hypoxaemia increases cerebral blood flow as measured by micro-
spheres by about 7–10 ml/100 g.min\(^{-1}\) mmHg \( P_{a,02} \) in unanaesthetized foetal lambs.

The relative weight of the brain is large in primates compared with other mammals. This accounts for the larger share of cardiac output and total \( O_2 \) consumption taken by the primate brain compared with relatively smaller ones. Tissue \( O_2 \) consumption is
however higher in sheep than in monkeys (Table 4). Perhaps this reflects the larger ratio of basal to cortical tissues in sheep.

Cerebral blood flow also increases with hypercapnia. Widely varying figures have been reported for this response. The figure of 3.6 ml. 100 g\(^{-1}\).min\(^{-1}\) from a particularly careful investigation may be representative (Jones et al. 1978). A value as low as 0.6 ml. 100 g\(^{-1}\).mmHg \(P_{a,CO_2}\) was obtained using a method which measures mainly cortical flow (Kjellmer et al. 1974).

It seems probable that blood pH and oedema may also influence cerebral vascular conductance in addition to the vasodilator actions of falling \(P_{a,CO_2}\), falling \(P_{a,O_2}\) and rising \(P_{a,CO_2}\) in asphyxia. Such multiple actions probably account for failure to observe any hypercapnic hyperaemia in foetal lambs at \(P_{a,O_2}\) below 20 mmHg (Kjellmer et al. 1974). Cerebral blood flow increased in isocapnic hypoxaemia \((P_{a,CO_2} \sim 15\, \text{mmHg})\). Blood pressure only rose 17% but brain flow \(\sim 88\%\). Cortical blood flow increased by \(\sim 79\%\) and brainstem flow by \(119\%\) of control values. Thus only a minor part of the increased cerebral flow during hypoxaemia can be accounted for by the accompanying increase of arterial pressure. Control levels of flow were regained 2\(\frac{1}{2}\) h after the end of a 90 min period of hypoxaemia. In asphyxia the brain stem and other non-cortical parts have been found to attract proportionately larger increases of blood flow than the cortex (Johnson et al. 1979; Ashwal et al. 1980).

Halothane anaesthesia of the ewe when the foetus was already very acidotic led to a further fall of cerebral \(O_2\) delivery in all regions, some of which must be attributable to the accompanying fall of arterial pressure in these extreme circumstances (Palahniuk et al. 1980).

Coronary circulation

In foetal lambs (120–140 days gestation) with chronically implanted catheters coronary blood flow in normoxia is about 150–200 ml. 100 g\(^{-1}\).min\(^{-1}\). Reduction of the \(P_{a,O_2}\), to \(\sim 12\, \text{mmHg}\) more than doubled blood flow (Ashwal et al. 1981; Cohn et al. 1974; Peeters et al. 1979). Similar hypoxaemia in foetal monkeys but under \(N_2O/halothane\) anaesthesia (Behrman et al. 1970) caused a non-significant increase of coronary tissue blood flow, but this response was complicated by accompanying hypercapnia and severe acidaemia. However, in both sets of experiments the coronary share of combined ventricular output was significantly increased from 2.7 to 4.9% in monkeys and from 2.5 to 6.8% in lambs.

When foetal cardiac output was raised after several days administration of triiodothyronine (\(T_3\)) coronary flow increased absolutely and also as a percentage of the increased cardiac output (Lorijn et al. 1980).

The enlarged hearts found in foetal lambs with raised blood pressures seven days
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Table 5. Myocardial blood flow in foetal lambs with normal and raised blood pressure (Fore, 1982)

<table>
<thead>
<tr>
<th>Heart weight (g)</th>
<th>Blood flow ml. 100 g⁻¹ min⁻¹</th>
<th>% CVO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control lambs</td>
<td>24.0</td>
<td>253</td>
</tr>
<tr>
<td>Hypertensive lambs</td>
<td>35.9</td>
<td>330</td>
</tr>
</tbody>
</table>

following bilateral nephrectomy not only received an increased proportion of a cardiac output within the normal range but had a raised tissue flow (Table 5; Fore, 1982).

Renal circulation

The kidney receives approximately 1.9% of the cardiac output in foetal lambs (Rudolph & Heymann, 1970) and 2.7% in foetal rhesus monkeys and baboons (Behrman et al. 1970; Paton et al. 1973). Renal vascular resistance is high and GFR low when expressed in terms of kidney weight (Loggie, Kleinman & Van Maanen, 1975). In foetal lambs GFR does not change between 90 and 130 days gestation when expressed in terms of kidney or body weight (Robillard et al. 1977; Robillard, Weismann & Herin, 1981), in spite of the concomitant rise of arterial pressure, cardiac output and structural maturation within the kidney. After 135 days there is a large increase in absolute GFR but not renal plasma flow (Hurley et al. 1977). In those species where nephrogenesis is still continuing at birth (e.g. rat, rabbit and pig) incomplete development of the vasculature may contribute to the high resistance to flow. However, resistance remains high in lambs until after birth, even though nephrogenesis is complete some time before parturition (Robillard et al. 1981).

Renin-like granules have been described in the juxtamedullary apparatus of foetal kidneys of several species including the human (see Mott, 1979; Smith et al. 1974). However, it is doubtful if angiotensin II is responsible for the normally low renal blood flow since infusion of the angiotensin II antagonist saralasin into conscious foetal lambs did not alter renal blood flow or vascular resistance (Iwamoto & Rudolph, 1979).

The changes of renal blood flow which follow hypoxaemia, hypercapnia and haemorrhage have been attributed to sympathetic vasoconstriction (Beguin, Dunnihoo & Quilligan, 1974; Campbell et al. 1967a; Dunne, Milligan & Thomas, 1972). Using microspheres to measure the distribution of cardiac output at an arterial \( P_{O_2} \) of first 20 and then 12 mmHg in unanaesthetized foetal lambs, it was observed that renal blood flow was reduced by 25% during hypoxaemia, and by 50% during asphyxia (Cohn et al. 1974). Peeters et al. (1979) found that renal blood flow was independent of arterial \( P_{O_2} \) values above 20 mmHg and that vasoconstriction occurred abruptly below this. The decrease of renal blood flow in foetal lambs was larger when the hypoxaemia was induced after inhibition of prostaglandin synthesis by foetal infusion of indomethacin (Millard, Baig & Vatner, 1979). Thus prostaglandins may be responsible for mitigation of foetal renal vasoconstriction following hypoxaemia.

Renal vasoconstriction during hypoxaemia can arise reflexly from stimulation of the aortic chemoreceptors (Campbell et al. 1967a; Dawes, 1968). However, hypoxaemia also increases the circulating concentrations of catecholamines and vasopressin (Jones
Infusion of either hormone at rates which produce plasma levels comparable to those observed during hypoxaemia does not alter renal blood flow (Robillard & Weitzman, 1980; Walker, 1977) although absolute GFR is increased. These observations suggest that both hormones preferentially increase post-glomerular resistance.

Hence the effects of hypoxaemia on the foetal renal circulation appear to involve the competing effects of neurogenic vasoconstriction and the relative maintenance of renal blood flow and GFR by the increase of arterial pressure and the intra-renal actions of prostaglandins, catecholamines and vasopressin.

The mature foetal kidney has a considerable capacity for the synthesis and excretion of prostaglandins from at least 0.5 of gestation (Pace-Asciak & Rangaraj, 1978; Mitchell, 1982). Despite the presence of high concentrations of these potent vasodilator substances (Challis et al. 1978), the kidney maintains an apparent high vascular resistance. Prostaglandins appear tonically to decrease resistance somewhat, since renal blood flow decreases after prostaglandin synthetase inhibition in unanaesthetized foetal lamb (Heymann & Rudolph, 1976, 1978). However, the direct effect of prostaglandins on the renal vasculature may be secondary to their influence on the intra-renal action of other hormones, such as vasopressin and angiotensin, and on the effects of sympathetic nerve activity (Millard et al. 1979).

Gastro-intestinal tract

Estimates of normal blood flow through the gut of unanaesthetized foetal lambs range from 52 to 288 ml.min⁻¹ 100 g⁻¹ (2.8–5.8% CVO) (Charlton, Reis & Lofgren, 1979; Cohn et al. 1974; Gilbert, 1980; Iwamoto & Rudolph, 1979; Peeters et al. 1979). Some of this variation may be due to differences of procedure. Peeters et al. (1979) showed that flow to the ileum and jejunum was greater than that to the stomach and colon.

Intestinal blood flow in foetal lambs fell sharply when the $P_{a,0}$ was less than 20 mmHg (Cohn et al. 1974; Peeters et al. 1979). It also fell following small (10%) increases or decreases of foetal blood volume (Gilbert, 1980).

Blood flow to the liver of unanaesthetized foetal lambs is high on account of the large contribution from the umbilical vein. It is clear that flow in the region of the portal sinus must be complex, and may be influenced by rhythmic changes in inferior caval pressure related to the cardiac cycle and foetal breathing movements.

The total blood flow through the liver of unanaesthetized foetal lambs, and the proportion received from the umbilical, hepatic and portal supplies, was not changed when the umbilical vein $P_{0}$ was reduced from 32 to 20 mmHg for 5–9 min. When umbilical blood flow was reduced 25–50% by partial occlusion of the dorsal aorta the umbilical contribution to liver and blood flow was reduced in proportion, but the hepatic and portal contributions and their distributions within the liver were unchanged. Further evidence also suggested that the partition of flows between the liver substance and ductus venosus was determined purely by the pressure differences across, and vascular resistance within, the liver and ductus venosus (Edelstone et al. 1980).
Vasoactive agents

Isolated mesenteric vessels from foetal lambs of 115–130 days gestation were more sensitive to both noradrenaline and 5-hydroxytryptamine than at ages nearer to term (Su et al., 1977). This similar change, with growth, in response to two different agonists suggests that maturational changes of the contractile elements of the muscle occur which are unrelated to the innervation. Intravenous infusions of noradrenaline (Lorijn & Longo, 1980) and angiotensin II (Iwamoto & Rudolph, 1981) into conscious foetal lambs which produce an elevation of arterial pressure of 8–12 mmHg did not alter intestinal blood flow as measured with microspheres. Infusion of the angiotensin II competitive inhibitor saralasin was also without effect although blood flow to other regions (e.g. skin, muscle, adrenals) increased (Iwamoto & Rudolph, 1979).

Adrenal gland

Measurement of blood flow by venous collection from adrenal glands in anaesthetized foals (Comline & Silver, 1972) led to the important observation that both splanchnic nerve stimulation and anoxia increased adrenal blood flow, although the possibility that this may have been partly due to the accompanying increases of blood pressure was mentioned.

Recent application of the microsphere technique has provided measurements of flow in normal and experimental situations in foetal sheep, but since the glands receive only about 0.1% of the cardiac output (Cohn et al., 1974) the number of spheres trapped is small. This limits the precision of some results, but in unanaesthetized sheep and monkeys adrenal blood flow is as great as in the adult. In foetal lambs this flow (~ 300 ml 100 g^-1 min^-1) appears to represent a minimum, since several dissimilar experimental manoeuvres all increase blood flow. Plasma angiotensin II may regulate adrenal blood flow since infusion of the hormone decreased flow (Iwamoto & Rudolph, 1981), whereas infusion of the antagonist saralasin increased flow (Iwamoto & Rudolph, 1979). Adrenal blood flow was increased during hypoxaemia, but this may only be secondary to the rise of blood pressure (Cohn et al., 1974). However, in this situation the increased flow might enhance the clearance of catecholamines and other hormones from the gland, and hence lead to a further increase of blood pressure and adrenal blood flow. Infusion of noradrenaline (Lorijn & Longo, 1980) and of vasopressin (Iwamoto & Rudolph, 1979) into unanaesthetized foetal lambs at relatively high rates did not alter adrenal blood flow. Presumably sufficient vasoconstriction occurred to counter the accompanying increase of arterial pressure. The small effects that vasoconstrictor substances and sympathetic nerve stimulation appear to have upon adrenal blood flow, in both the foetus and adult, suggest that this organ does not participate in these generalized compensatory reactions. This is perhaps appropriate, since maintenance of adequate blood flow through the gland would be required.

Thyroid

The fraction of cardiac output distributed to the thyroid of the foetal lamb ranged from 0.06 to 0.11% of the combined output of both ventricles (Iwamoto & Rudolph,
Administeration of saralasin increased tissue blood flow from 170 to 329 ml.·100 g⁻¹·min⁻¹ despite a small fall of arterial pressure. Infusion of angiotensin II increased arterial pressure but decreased thyroid blood flow from 147 to 84 ml.·100 g⁻¹·min⁻¹. Foetal lambs treated with tri-iodothyronine (2 ng·l⁻¹ plasma) had arterial pressures in the normal range, but thyroid blood flow was little more than half that in untreated lambs despite a large increase of cardiac output (Lorijn et al. 1980). Whether this last response is due to increased sympathetic activity or increased concentration of circulatory vasoconstrictor substances is unknown.

### Skin, skeleton and skeletal muscle

Less than one-fifth of the foetal cardiac output is accounted for by blood flow to the brain, heart, kidney and gastrointestinal tract. Moreover, these organs jointly receive less than one-third of the arterial flow to the foetal body. Detailed information is lacking about the circulation to the remainder, which comprises mainly skin, skeletal muscle, fat, bone and spinal cord. Many studies have calculated flow to the foetal body after removal of the viscera, and as such the carcass appears to receive at least...
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Table 6. Distribution of blood flow to systemic vascular beds in foetal lambs (I. M. Fore, unpublished)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Cardiac output (CVO) (%)</th>
<th>Systemic flow (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>G.I. tract</td>
<td>6.5</td>
<td>16.0</td>
</tr>
<tr>
<td>Liver (arterial)</td>
<td>0.4</td>
<td>28.4</td>
</tr>
<tr>
<td>Spleen</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Adrenals</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Lungs</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>8.6</td>
<td>35.7</td>
</tr>
<tr>
<td>Carcass</td>
<td>27.1</td>
<td>63.2</td>
</tr>
</tbody>
</table>

Table 7. Change of blood flows (ml.kg body weight⁻¹.min⁻¹) during hypoxaemia (PaO₂ 12-15 mmHg) in foetal lambs estimated from distribution of microspheres introduced into the arterial system or the umbilical vein

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Arterial system</th>
<th>Umbilical vein</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td>Myocardium</td>
<td>18.5</td>
<td>8.9</td>
</tr>
<tr>
<td>Brain</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>G.I. tract</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Kidneys</td>
<td>3.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Lungs</td>
<td>9.7</td>
<td>4.2</td>
</tr>
<tr>
<td>Carcass</td>
<td>45.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60.7</td>
<td>20.2</td>
</tr>
<tr>
<td></td>
<td>16.3</td>
<td></td>
</tr>
</tbody>
</table>

(a) Cohn et al. (1974).
(b) Reuss & Rudolph (1980).

20% of the cardiac output, or over 50% of the flow to the foetal body (Rudolph & Heymann, 1970). Since muscle may account for only about half of the weight of a carcass (Creasy et al. 1973), a considerable fraction of this flow is probably directed to bone and skin (Fig. 1, Table 6). In adult animals, blood flow to the skeleton accounts for 3–7% of the cardiac output (Copp & Shim, 1965; Tothill & McCormick, 1976), and the bone of growing animals may reasonably be expected to receive at least this proportion.

In anaesthetized foetuses microsphere studies have shown that blood flow to the carcass decreased during acute hypoxia, and this was greater when acidaemia accompanied the hypoxaemia (Cohn et al. 1974). Flow to the carcass only fell at PaO₂ < 20 mmHg (Peeters et al. 1979). However, since the carcass accounts for about a half of the systemic blood flow even moderate vasoconstriction is adequate to divert a considerable fraction to other regions which dilate during hypoxaemia (see Table 7).

Blood flow to the soleus (a slow) and gastrocnemius (a fast) muscle was found to be
and 14.0 ml. 100 g^-1.min^-1 respectively (Molteni et al. 1980), and this similarity shows that the higher basal flow rate of slow muscle, which is characteristic of the adult (Hilton, Jeffries & Vrbova, 1970), is not present in the foetus. During non-breathing periods flow to the foetal diaphragm was comparable to that of adult sheep during quiet breathing, whereas foetal intercostal muscle flow was three times greater than the adult. During vigorous breathing induced by intravenous infusion of acid (NH₄Cl or HCl 20–25 mM.kg^-1) to the foetal lamb, blood flow to the diaphragm and chest wall increased 6–12 times (Molteni et al. 1980), exceeding the changes occurring in adult sheep during heat stress (Hales, 1973).

In foetal lambs delivered by Caesarean section under light chloralose anaesthesia, section of the sciatic nerve resulted in an increase of femoral flow, indicating that in these circumstances the hind-limb circulation was under a degree of vasoconstrictor control (Dawes et al. 1968). The hind-limb vascular resistance increased progressively from 90 to 140 days of gestation. Asphyxia and hypoxia caused vasoconstriction which was considerably attenuated by section of the vagi, and the response was thus attributed to stimulation of the aortic chemoreceptors. After a careful search for any contribution from carotid chemoreceptors, their participation in reflex hypoxic vasoconstriction was concluded to be minimal or absent (Dawes et al. 1968, 1969). Variations of arterial blood gases produced by ventilating the foetal lambs with gas mixtures of various compositions had also shown that femoral flow was sensitive to changes of arterial $P_{O_2}$ within the normal range (Campbell et al. 1967a). Reflex vasoconstriction of the hind-limb vasculature could be demonstrated from about 105 days gestation and was larger in older lambs. This provides a mechanism for the diversion of blood flow away from skeletal muscle during hypoxaemia and asphyxia (see Table 7).

**Pulmonary circulation**

The central feature of the circulatory transition accomplished at birth is a dramatic increase in pulmonary vascular conductance with reversal of the direction of blood flow through the ductus arteriosus (Dawes et al. 1953).

In the lamb in utero, although pulmonary blood flow can vary and is reduced in hypoxaemia it does not exceed 5–6% of the combined output of both ventricles as measured by microsphere techniques in conscious preparations with chronically implanted catheters.

Direct effects of blood gas changes on pulmonary blood flow have been examined by perfusion of a non-ventilated (foetal) lung with blood equilibrated with appropriate mixtures of $O_2$, $CO_2$ and $N_2$ by a donor lung. Blood gas tensions ($P_a, CO_2$ 27 mmHg, $P_a, CO_2$ 42 mmHg) representative of those normally found in foetal lungs, can be attained by equilibration with a gas mixture containing 3% $O_2$ and 7% $CO_2$ in $N_2$. The dilatation achieved by hyperoxia and hypocapnia in the foetal condition is still far short of that attained with ventilation with gas (Dawes, 1969). Asphyxial vasoconstriction has been demonstrated as early as 0.5 term and is not dependent on innervation of the lungs (Campbell et al. 1967b). This is analogous to the principal vasoconstrictor action of hypoxic ventilation in the adult. While reflex vasoconstriction could be blocked with hexamethonium (Campbell et al. 1967b), $\alpha$ and $\beta$ adrenoceptor blockers were found not to influence the pulmonary vascular response to hypoxaemia in
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chronically catheterized foetal lambs (Lewis et al. 1976). This suggests that the direct effects of hypoxaemia on the pulmonary vasculature are of predominant importance in the intact foetus.

During maternal hypoxaemia the fraction of cardiac output going to the foetal lungs was reduced from 10-7 to 3-2% in monkeys and from 3-9 to 1-9% in lambs (Behrman et al. 1970; Cohn et al. 1974).

Nervous control of the pulmonary vasculature

Electrical stimulation of the peripheral cut end of the vagus causes pulmonary vasodilatation, and stimulation of the cardiac sympathetic nerves to the foetal lung causes vasoconstriction (Colebatch et al. 1965). Although the sympathectomized lung is more vasodilated than the intact lung nevertheless pulmonary ventilation with 3% O₂ and 7% CO₂ (which avoids change of gas pressures in the perfusing blood) still substantially increases pulmonary conductance (Dawes, 1969).

Stimulation of the sympathetic supply to the left lung causes profound pulmonary vasoconstriction as early as 0-6 term. By 0-68 of term it has been shown that pulmonary vasoconstriction can be reflexly activated in a foetal lung itself perfused with normal foetal blood (Campbell et al. 19676).

Vasoactive substances

The high vascular resistance of the foetal lung is reduced by acetylcholine in μg doses which have minimal effects on the circulation of a ventilated lung. In chronically catheterized foetal lambs sensitivity to acetylcholine increases with age (Lewis et al. 1976). Histamine (Dawes & Mott, 1962), bradykinin (Cassin et al. 1964a) and isoprenaline (Cassin et al. 1964b) also cause pulmonary vasodilatation in anaesthetized exteriorized preparations.

Angiotensin II increases and saralasin decreases pulmonary vascular conductance in foetal lambs (Iwamoto & Rudolph 1979, 1981). It has been suggested that angiotensin II might release vasodilator prostaglandins in the pulmonary vessels. However, it is possible that systemic venous and hence pulmonary arterial O₂ are increased as a result of increased systemic blood flow (Table 3) with the net result of vasodilatation in the lung circulation. Indeed, in some species it has been found that angiotensin II is necessary for hypoxic vasoconstriction (Berkov, 1974). Nevertheless foetal pulmonary blood flow can increase dramatically above 2 mM O₂ (~ P₀₂, 13 mmHg; Peeters et al. 1979). It is also significantly raised during prolonged treatment with tri-iodothyronine (Lorijn et al. 1980).

Prostaglandin E₂ is a potent vasodilator of the goat foetal pulmonary circulation, with 50% of maximal response obtained by infusion of 1-6 μg.kg⁻¹ (during 1 min) (Cassin, Tyler & Wallis, 1975). However, administration of indomethacin (an inhibitor of prostaglandin synthetase) did not significantly affect the pulmonary vascular resistance of foetal goat lung perfused at constant flow.

The mechanisms of hypoxic vasoconstriction (which do not depend on neural mediation) remain a matter of contention even in the adult (Barer, 1981). By adult standards the normal foetal lung is vasoconstricted and is far more sensitive to vasodilator agents, as mentioned earlier, than the adult lung. Prolonged reactive
hyperaemia follows pulmonary arterial occlusion (Dawes, 1968). Ischaemia must exacerbate an already asphyxial situation and yet prolonged vasodilatation ensues. Various other manoeuvres also prevent pulmonary hypoxic vasoconstriction (e.g. injection of cyanide). No consensus as to a final common pathway for pulmonary hypoxic vasoconstriction has been achieved.

Vascular shunts and redistribution of cardiac output

Ductus venosus

In some species a half or more of the umbilical venous return bypasses liver tissue either, as in the lamb, through a relatively large vessel (Edelstone et al. 1978) or, as in the pig, through channels which permit passage of microspheres 15 µm in diameter which would be trapped by capillaries. In contrast no extrahepatic channel has been demonstrated between the umbilical vein and inferior cava in the foal (Barnes et al. 1979). There is no evidence that the ductus venosus, when present, regulates blood flow to the liver (Edelstone et al. 1980).

Foramen ovale

This passage in the foetal lamb allows well-oxygenated inferior caval blood to reach the left atrium directly without passing through the lungs. The fall of inferior caval and rise of left atrial pressure caused by increased pulmonary blood flow when breathing begins presses the semi-cylindrical membranous valve of the foramen against the crista dividens, thus preventing right-to-left shunting at this level in the newborn animal (Dawes et al. 1955). The progress of anatomical closure varies with the species (Dawes, 1968).

Ductus arteriosus

This short but wide remnant of lateral dorsal aorta forms a direct continuation of the pulmonary trunk which discharges into the descending aorta. Flow through it is from right to left in foetal life, with diversion of blood from the relatively high-resistance pulmonary circulation. The pressure drop along the ductus is small (~ 2 mmHg) but increases when constriction is induced by the prostaglandin synthetase inhibitors indomethacin or acetylsalicylic acid (Heymann & Rudolph, 1976; and see Mott, 1980). At birth blood flow through the ductus reverses following the fall of pulmonary artery pressure consequent upon pulmonary vasodilatation due to ventilation.

Redistribution of blood flow

Reduction of $P_{a,o_{2}}$ from 21 to 12 mmHg reduced cardiac output from 464 to 442 ml.kg$^{-1}$.min$^{-1}$ and systemic conductance by 28% (Table 3). Arterial blood flow to the heart and brain were increased by ~ 29 ml.kg body weight$^{-1}$.min$^{-1}$, which was only half the fall of flow measured in the gut, kidneys, lungs and carcass combined (Table 7a). In another investigation in which $P_{a,o_{2}}$ fell from 24 to 15 mmHg, cardiac output was reduced from 505 to 414 ml.kg$^{-1}$.min$^{-1}$ and systemic/umbilical flow ratio from 1.66 to 0.69, a corresponding redistribution of umbilical venous blood
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occurred (Table 7b). It is clear that provision for increased perfusion of heart and brain (which together form ~ 2% body weight) can be accommodated by a very limited degree of vasoconstriction in an organ such as skeletal muscle which constitutes a significant proportion of body mass (Campbell et al. 1967a; Dawes et al. 1968).

It is probable that the aortic chemoreceptors play a part in the redistribution of cardiac output in the foetus during hypoxia (Campbell et al. 1967a; Dawes et al. 1968). The threshold for foetal baroreceptor stimulation appears to be above the normal range of arterial pressures (Dawes et al. 1980). The small increases in arterial pressure which accompany hypoxaemia or asphyxia would not per se be expected to lengthen the heart period.

Experimental procedures designed to retard foetal growth in lambs have produced deviations from normal of cardiovascular function. Placental embolism caused by repeated doses of non-radioactive microspheres reduced placental conductance substantially but systemic conductance was unchanged. However, flow to the carcass was 27% lower, while that to the brain and heart were, respectively, 65% and 89% higher than in control animals (Creasy et al. 1973). These differences are probably largely due to the low $P_{a, O_2}$ (17 mmHg) in the embolized lambs compared with 23 mmHg in the control lambs. The redistribution of flow resembles that caused acutely by hypoxaemia (Table 7), though the cardiac output per kilogram was comparatively lower than that seen during acute hypoxaemia. Comparable hypoxaemia accompanied by polycythemia and hypoglycaemia were found in lambs conceived in ewes previously subjected to carunculectomy (Robinson et al. 1979).

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REFERENCES


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