Vasomotor Responses in the Hindlimb of Newborn Calves

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ABSTRACT

The reflex control of the hindlimb circulation was examined in 9 newborn calves under chloralose anesthesia by measuring iliac arterial pressure-flow curves. Asphyxia always caused vasoconstriction which was abolished or greatly reduced by sciatic nerve section. Vasomotor tone was present a few hours from birth, as shown by an increase in flow on sciatic nerve section and by drug action. It is concluded that autonomic control of the systemic circulation is effective in this species at birth.

ADDITIONAL KEY WORDS
asphyxia  vasoactive drugs  pressure-flow curves

There is increasing experimental evidence that the heart and circulation in the newborn is under reflex control by the autonomic nervous system. The presence of tonic baroreceptor activity (1, 2), and neural control of heart rate seem clearly established (3). Downing et al. (4) observed an increase in left ventricular contractility, heart rate and systemic vascular resistance on reducing brachiocephalic perfusion pressure in the newborn lamb. They inferred that this was due to an increase in sympathetic activity; ganglionic blockade abolished these responses. Campbell et al. (5) found evidence of reflex vasoconstrictor activity in the pulmonary circulation of asphyxiated mature fetal lambs; this was abolished by cutting the efferent sympathetic nerves. Campbell et al. (6) suggest that small changes in blood gas tensions cause a redistribution of systemic blood flow in the mature fetal lamb.

In the newborn dog, however, Boatman et al. (7) found that stimulation of the lumbar sympathetic chain did not cause vasoconstriction in the hindquarters in the first 2 weeks after birth. The sensitivity to vasoconstrictor agents appeared to increase with age. Young (8) also has questioned whether effective reflex vasoconstriction can take place in the systemic circulation of the newborn human.

The present investigation was designed to study the vasomotor responses of the circulation in the hindlimb of the newborn calf during asphyxia, before and after interruption of the sympathetic supply. The newborn calf was chosen because it is a large animal and because Comline and Silver (9) reported that the innervation of the adrenal medulla in this species is incomplete at birth, as judged by the relatively small output of catecholamines on splanchnic stimulation.

Methods

Nine newborn calves, 5 to 48 hr old, were lightly anesthetized with chloralose (30 mg/kg iv). The normal variation in duration of pregnancy is small in the variety of cows used (9 months ± 10 days), and the relatively small...
FIGURE 1

Schematic diagram of extracorporeal circuit, including an electromagnetic flowmeter and vertical tube, for measuring flow and generating pressure-flow curves in the hindlimb.

variation in weight of the calves used (Table 1) suggests that none were unusually premature. Rectal temperature was maintained at 38 ± 1°C. Preliminary studies indicated that adequate gas exchange was not maintained while the calves were in the supine position and breathing spontaneously. Therefore they were ventilated through a tracheal tube by positive pressure from a Starling Ideal pump using either room air or oxygen-enriched air (3 to 4 liters O₂/min flowing past the air inlet). Asphyxia was produced by stopping the respiration pump and clamping the tracheal tube. The sciatic nerve was isolated as it emerged from the pelvis. A segment of the external iliac artery about 2.5 cm in length was exposed and its side branches were tied. Heparin (10 mg/kg) was injected intravenously. The vessel was divided and the cut ends rejoined by an external loop of plastic materials—polyvinyl, polyethylene, and perspex (Fig. 1). In 3 calves ligatures were tied around all tissues except the iliac vessels and sciatic nerve to interrupt collateral vessels. This did not alter pressure-flow relations in the limb.

Mean and phasic arterial pressures were measured in the flow loop with calibrated strain-gauge transducers. Blood flow was measured with a cannulated electromagnetic flowmeter (10) which has a baseline error <1% and variation in sensitivity <2% of scale (200 ml/min) over 5 hr. Arterial pressures (iliac and brachial), blood flow and heart rate (11) were recorded continuously on a direct-writing multichannel recorder (Schwarzer).

Changes in vasomotor tone were measured as described by Cassin et al. (12). The slope and intercept of the pressure-flow curve on the pressure axis were calculated. The output of the flowmeter was displayed on the Y-axis and that of the manometer on the X-axis of an X-Y recorder. Arterial pressure-flow curves were obtained by filling the vertical tube (Fig. 1) with blood and allowing this blood to flow into the hindlimb while the inflow to the loop was temporarily interrupted. On each occasion, the tube, which had been clamped off, was filled immediately before the pressure-flow curve was obtained. The average curve took only 10 to 15 sec to run, so that the composition of the blood in the tube was comparable to that in the rest of the animal. Such records showed a smooth fall in flow as pressure decreased (Fig. 3).

In 1 newborn calf (no. 6 of Table 1) both iliac arteries were isolated, and a cuff electromagnetic flowmeter (i.d. 6 mm) (13) was placed around one iliac artery while the artery of the other side was cannulated as in Figure 1. This allowed simultaneous recording of pressures and flows in an innervated and denervated hindlimb in the same animal. Blood flow in the carotid artery was determined in 2 calves by placing a cuff electromagnetic flowmeter (i.d. 10 mm) around the left carotid. This allowed a comparison of carotid and hindlimb blood flow during asphyxia. The cuff electromagnetic flowmeter had a baseline error <2% and variation in sensitivity <3% of scale (200 ml/min); it was one that did not require calibration in use.

Blood samples were collected anaerobically from a cannulated brachial artery. They were analyzed at once using a Radiometer ultramicro electrode assembly. The values were corrected for the difference in temperature between the electrodes and the rectum.

Intra-arterial injections of tyramine HCl, norepinephrine-bitartrate, acetylcholine perchlorate, histamine acid phosphate, bradykinin (Sandoz) and angiotensin (Sandoz) were administered.

Results

The majority of hindlimb preparations in newborn calves (8/9) were accomplished without any technical problems. However, in 3 calves, a transient episode of hypotension, bradycardia and intense systemic vasoconstriction was seen. This occurred after the abdomen was opened, and usually shortly after insertion of the iliac loop; there was a

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Initial Values in Newborn Calves

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (hr)</th>
<th>Weight (kg)</th>
<th>( pH )</th>
<th>( P_{O_2} ) (mm Hg)</th>
<th>( P_{CO_2} ) (mm Hg)</th>
<th>Characteristics of iliac pressure-flow curve</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>40</td>
<td>7.33</td>
<td>74</td>
<td>36</td>
<td>28 4.8</td>
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<tr>
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<td>7.33</td>
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<td>36</td>
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</tr>
<tr>
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<td>7.37</td>
<td>61</td>
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<td>29 5.5</td>
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<tr>
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<td>28</td>
<td>7.38</td>
<td>59</td>
<td>37</td>
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<tr>
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<td>36</td>
<td>7.39</td>
<td>50</td>
<td>36</td>
<td>28 3.0</td>
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<tr>
<td>6*</td>
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<td>35</td>
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<td>33</td>
<td>22 5.4</td>
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<tr>
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<td>47</td>
<td>34</td>
<td>7.34</td>
<td>64</td>
<td>39</td>
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</tr>
</tbody>
</table>

*Intercept of linear portion of pressure-flow curve on the pressure axis.
†Slope of linear portion expressed as ml/min per kg body weight of calf and per 100 mm Hg.
**Pressure-flow curves were not recorded in this calf, in which blood flow was measured in both iliac arteries.

**RESPONSE TO ASPHYXIA WITH THE SYMPATHETIC INNERVATION TO THE HINDLIMB INTACT**

Table 1 shows the initial measurement on 9 newborn calves. Under the experimental conditions chosen there was no evidence of a systematic variation in the iliac arterial pressure-flow curves with age from birth.

Asphyxia was induced on 19 occasions for fall in arterial \( P_{O_2} \), while \( pH \) increased and \( P_{CO_2} \) fell. Increasing the concentration of oxygen in the gas mixture used for positive pressure ventilation did not immediately reverse the situation, although small infusions (100 ml) of dextran (6% in 0.9% saline solution, Intradex) seemed to improve it. Recovery was spontaneous within 30 min. Subsequent experiments suggest that this phenomenon may have been due to manipulation of the peritoneum and intestines (Dawes, personal communication).
The figures indicate the means ± se. Control figures were calculated as the means of observations made shortly before and after full recovery from asphyxia. *As defined in legend to Table 1.

The sciatic nerve carries most of the sympathetic nerve fibers to the hindlimb. On sciatic nerve section in 8 of the 9 newborn calves, the iliac arterial blood flow increased within 10 sec, without any change in mean arterial blood pressure. There was a 43% mean increase in the slope of the pressure-flow curve indicating that there had been some resting vasoconstrictor tone (Table 2A, B). The 1 calf (no. 7) that did not have a fall in hindlimb vasomotor tone was 1 of the 3 that had previously experienced a 30-min episode of hypoxemia, hypotension and bradycardia with an alkaline pH and decreased arterial Pco₂. Intense hindlimb vasoconstriction had occurred followed by vasodilatation, and it was at this point that nerve section was performed. All reflex vasoconstrictor tone had apparently been abolished before nerve section; yet this animal had responded by active hindlimb vasoconstriction to asphyxia as well as to the pressure-flow curves during asphyxia.
transient episode of hypotension and bradycardia.

The 9 calves were asphyxiated 23 times after sciatic nerve section. In each instance the duration of asphyxia was identical with that before nerve section. This produced comparable blood gas tensions and pH during asphyxia as shown in Table 2B. In every instance the vasocostriction observed before nerve section was either abolished or greatly reduced (Figs. 2, 3 and 4; Table 2B). In 2 calves, section of the femoral nerve to the same limb caused no further change in the pressure-flow curves, either before or during asphyxia. In neither of these calves had sciatic nerve section completely abolished asphyxial vasoconstriction. It seemed possible that some sympathetic fibers might enter the hindlimbs by another route. Since section of the femoral nerve failed to alter the response, it is excluded as a possible pathway.

The patterns of vasomotor response to asphyxia were also compared in a calf (Table 1, no. 6) in which arterial pressure and blood flows were recorded in both iliac arteries simultaneously (Fig. 2). When the sympathetic innervation to the hindlimbs was intact, the asphyxia caused a decrease in iliac flow bilaterally while mean arterial pressure was
Newborn calf. Records of arterial pressure (top) and of iliac flow (bottom) on injection of acetylcholine (Ach), norepinephrine (Norad) and tyramine (Tyr) into the iliac artery.

Discussion

The increase in vasomotor tone of the hind-limb during asphyxia was measured either by observing the alteration in arterial pressure and iliac flow (as in Fig. 2) or the alterations in arterial pressure-flow curves (as in Fig. 3). The latter method is to be preferred since the pressure-flow curves in the calf's hindlimb are not linear through the origin. Calculation of vascular resistance as the quotient of pressure and flow (dP/dQ) is therefore a less sensitive and sometimes misleading indicator of vasomotor tone. For technical reasons the pressure-flow curves were run over a pressure range (70 to 40 mm Hg) somewhat less than that which normally obtains in newborn calves during asphyxia. In other species pressure-flow curves run over a large range of pressures have given reliable and reproducible results before and during asphyxia, provided that the curves were always run over a similar pressure range. In the present experiments, venous pressure was not measured because the arterial pressures were so high, particularly during asphyxia (e.g., Fig. 2), that changes in venous pressure would be of little consequence.

There are several physiological mechanisms activated in response to asphyxia, which may function singly or in combination. Asphyxial vasoconstriction may operate via the systemic arterial chemoreceptors or by direct stimulation of higher centers in the central nervous system or both. Daly and Ungar (18), using a
technique which allowed perfusion of the aortic and carotid bodies in the dog with blood of varying oxygen tensions, observed that vasoconstriction may occur with either hypoxic stimulation of the aortic body or carotid body provided the respiratory-induced vasodilator reflex was controlled. Other workers have shown that hypoxia (19, 20) or hypercapnia (19) in the central nervous system, after bilateral arterial chemoreceptor denervation, causes an increase in systemic vascular resistance in adult dogs. No attempt was made in the present experiments to distinguish between these possibilities, but one point must be made. When a calf is asphyxiated it makes strong respiratory efforts which could influence the result. Yet, as Campbell et al. (6) showed, asphyxia causes hindlimb vasoconstriction in anesthetized fetal lambs in the absence of respiratory movements. The effect of gasping is therefore likely to be of minor importance.

The level of hypoxemia and hypercapnia attained during asphyxia of newborn calves barely exceeded normal fetal levels (9) (Po2 34 ± 4.6, Pco2 52 ± 2.9, pH 7.29 ± 0.02). Yet this degree of asphyxia caused intense vasoconstriction after birth. This response is mainly dependent upon the integrity of sympathetic fibers carried in the sciatic nerve. There are many accounts of a similar mechanism in the limbs of adult animals. For instance, Bernthal (21) observed vasoconstriction in the forelimbs of adult dogs when blood equilibrated with 15% oxygen or less was perfused through the carotid bifurcations. The sympathetic outflow was the sole efferent pathway of this hypoxia-induced vasomotor reflex (22). In the cat also, Celander (23) found that the sympathetic nervous components dominated the response, as compared with the release of catecholamines into the circulating blood. Sympathectomy almost completely abolished the vasoconstrictor response to asphyxia in skin, skeletal muscle, kidney and spleen. Celander (24), using a plethysmograph, also observed vasoconstriction of the skin and muscle blood vessels in the foot and calf of newborn human infants after asphyxia.

By contrast, in puppies, Boatman et al. (7) did not see vasoconstriction (as measured by changes in pressure during constant flow perfusion of the aorta below the kidneys) on stimulation of the lumbar sympathetic chain up to 2 weeks after birth. They stimulated at a frequency of 20 cycle/sec which is high even for adult sympathetic nerves (23), and may have been ineffective on that account. The question of species differences in regard to the presence or absence of vasomotor control in the newborn remains open. In the newborn calf our observation that there is a vigorous reflex vasoconstriction in the hindlimb contrasts with the report by Comline and Silver (9) that the adrenal medulla does not respond effectively to asphyxia or to splanchnic nerve stimulation.

The importance to the newborn of a reflex mechanism for hindlimb vasoconstriction during asphyxia is that it assists in the regional redistribution of cardiac output. During asphyxia there is intense vasoconstriction in skin, skeletal muscle and lungs, while there is vasodilatation in the heart and brain (6). Thus, blood flow to the most vital areas is maintained at the expense of those of less immediate importance, such as the hindlimbs. These observations also support the concept that autonomic nervous control of the heart and blood vessels is effectively operative in the newborn.

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References


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