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CIRCULATORY RESPONSES TO ASPHYXIA IN PREGNANT AND FETAL ANIMALS: A COMPARATIVE STUDY OF WEDDELL SEALS AND SHEEP

Diving mammals share with fetal and newborn animals a high resistance to asphyxia when compared, respectively, with terrestrial and adult animals. Adaptations for conservation or sparing of oxygen and for adjustment to the effects of accumulated metabolic products, such as carbon dioxide and hydrogen ions, have been discovered in both diving marine mammals and asphyxiated terrestrial species. The major requirement in all instances of prolonged oxygen deprivation is for protection of the least resistant vital organs, the brain and the heart.

Dawes has recently reviewed the evidence supporting the view that integrity of the circulation contributes importantly to survival time of the asphyxiated fetus or newborn.[1] The mechanism is dependent on the concentration of glycogen in cardiac muscle before the asphyxial episode,[2] and requires an adequate circulatory supply of glucose to the brain for glycolytic energy production. Survival is shortened by blocking glycolysis with iodoacetate and prolonged by the administration of additional glucose when accompanied by base to maintain near normal pH.[3] The brain of the newborn dog also has a specific resistance to total ischemia, which enables it to survive longer than the similarly treated adult brain.[4]

Scholander suggested that fetal animals may react to asphyxia in a manner like that of adult diving seals[5] which experience a profound reduction and redistribution of cardiac output such that oxygen stored in blood is preferentially directed to the cerebral and coronary circulations. Selective vasoconstriction produces marked decreases in muscle, skin, mesenteric and renal blood flows, which are accompanied by bradycardia and little change in central arterial blood pressure. These events and similar ones in diving or asphyxiated land mammals, including man, are well documented and have recently been reviewed.[6,7] Similar, though less profound, changes in distribution of cardiac output have recently been demonstrated in partially asphyxiated, anesthetized lambs delivered by Caesarean section.[8]

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A prolonged dive by a pregnant marine mammal probably represents an extreme example of both fetal and maternal adaptation to asphyxia. It was the purpose of these experiments to investigate some circulatory aspects of this adaptation and its possible manifestations in non-diving mammals. Pregnant antarctic Weddell seals, *Leptonychotes weddelli,* were compared with pregnant sheep with regard to maintenance of uterine blood flow during asphyxia. Comparative fetal adjustments to asphyxia were studied by determinations of abdominal aorta blood flow and heart rate of fetal lambs *in utero* and heart rate of fetal seals during maternal asphyxia.

More is known about the natural history of diving in Weddell seals than in any other species of marine mammal. A maximum submersion time of 43 minutes and maximum depth of 600 meters have been recorded.[9] It has also been shown that near-term pregnancy did not restrict the diving ability of these animals. Maximum durations (up to 60 minutes) were even longer than in nonpregnant seals.[10] Weddell seals were chosen as the experimental diving animals in this study because of the abundance of information about their diving characteristics, their predictable breeding habits, and the convenience and ease with which they can be captured and managed.

METHODS

Seals

Experiments on Weddell seals were performed at the McMurdo Sound Station of the U. S. Antarctic Research Program. The animals appear in large numbers during October in seasonal colonies on sea ice near the shore. During that period they spend many days at a time lying on the ice where the pups are born. Mothers generally remain with the pups most of the time until weaning at an age of about six weeks. They first enter the water at three or four weeks after birth. Pupping reaches a peak late in October and continues during early November. Adult female Weddell seals are ordinarily about 2.5 meters long and weigh about 400 kg., but they are docile and are easily captured. Positive verification of pregnancy was obtained by drug immobilization and vaginal examination or by detection of the fetal electrocardiogram. Immobilization was found to be safely produced by intramuscular injection of a mixture of 0.3 mg/kg. phencyclidine (Sernylan,® Parke Davis) and 0.2 mg/kg. propionyl phenothiazine hydrochloride (Tranvet,® Diamond Labs.).

Following examination, the seal was transported by tractor to a laboratory hut located on the sea ice near the colony. It was dragged into the hut by tractor power, intubated and anesthetized with halothane gas combined with oxygen. The mixture was administered via a Fluotec vaporizer and a Bird Mark IX respirator equipped with a device for simulating the prolonged apneustic plateau breathing of the seal. The immobilizing drugs mentioned were usually insufficiently relaxing for intubation, and they were replaced on some occasions with succinylcholine chloride injected intramuscularly in a dose of about 5 mg/kg. Halothane administration was begun during the early stages of recovery from the effects of succinylcholine, and a level of about one percent in oxygen provided suitable surgical anesthesia.

Doppler ultrasonic blood flow transducers[11] were implanted aseptically around the uterine artery in four animals in an advanced state of pregnancy. There was no obvious difference in development of the arterial structures on either side of the uterus. In each instance the artery fit snugly within an 8 mm. inside diameter transducer. The exact age of the fetus could not be determined, but all were near maturity and within a few days or weeks of term. One animal was instrumented for comparative purposes by placement of an 8 mm. Doppler flow transducer on the renal artery. It has been shown in harbor seals that renal blood flow is profoundly reduced in response to diving asphyxia.[12]

After two or three days of recovery from surgery, during which time the animals were maintained in a plywood pen on the sea ice, diving experiments were performed. Experimental asphyxia was produced by a procedure in which the immobilizing agent, succinylcholine chloride, was used. The drug was injected intramuscularly in dosages of 5 to 10 mg/kg., thus producing paralysis, including that of respiratory muscles. An endotracheal tube was introduced into the airway, and respiration was artificially maintained with the Bird Mark IX respirator. In some experiments arterial blood PCO_2, PO_2 and pH were determined on a Radiometer blood gas apparatus, PH M27, and gas monitor, PHA 927, to estimate the appropriate respirator levels. Apnea was produced by disconnecting the respirator and simultaneously clamping the endotracheal tube.

The blood velocity signal, directly proportional to blood flow, was recorded on a Uher 4000 Report-L portable tape recorder for later transcription to paper on a Sanborn recorder. In some experiments the fetal heart rate was recorded on a portable Sanborn electrocardiograph by suitable placement of needle electrodes on the maternal abdomen.

Sheep

Comparative experiments were performed on pregnant Rambouillet-Suffolk crossbred sheep and fetal or newborn lambs. The effects of asphyxia of near-term pregnant ewes on blood flow in the middle uterine and renal arteries and fetal abdominal aorta *in utero* were tested by means of chronically implanted Doppler ultrasonic transducers. Surgery was performed using spinal anesthesia (lidocaine) in the ewe. Fetal surgery was accomplished by temporarily exteriorizing the uterus through a paramedial inguinal incision in the lower abdomen of the ewe and subsequent uterine incision. In most instances the procedure was performed while the fetus remained within the uterus. Local anesthesia with lidocaine was employed during fetal surgery. Eight fetal lambs ranging in gestational age from 120 to 135 days were instrumented by this procedure. Two aborted prematurely, four delivered normally and two were delivered by Caesarean section two or three days before the calculated parturition date (147 days). All lambs except the two that aborted were healthy and of normal birth weight.

Asphyxia experiments were performed on newborn and near-term lambs delivered by Caesarean section, both instrumented with Doppler ultrasonic blood flow transducers on the abdominal aorta. Observations were performed on two lambs born with previously implanted flow transducers. Four other lambs were instrumented immediately before delivery and were used in acute experiments involving umbilical cord clamping. Good acoustic coupling between transducer and artery was assured by lining the transducer with agar before implant. Altogether 24 pregnant ewes of known stage of gestation were used in various experiments.

Asphyxia was produced in pregnant ewes by immersion of the head in a plastic bag of water for 30 to 90 seconds. In all instances recovery from this procedure was prompt and complete. In those experiments in which near-term lambs were delivered by Caesarean section, breathing was prevented by inserting the lamb's head into a surgical glove filled with warm saline immediately after its removal from the uterus. The umbilical cord remained intact and functional until asphyxia was produced by clamping it with padded intestinal forceps. With care this cord-clamping procedure could be repeated several times, recovery being monitored by restoration of abdominal aorta flow in the fetus.

RESULTS

Weddell seals

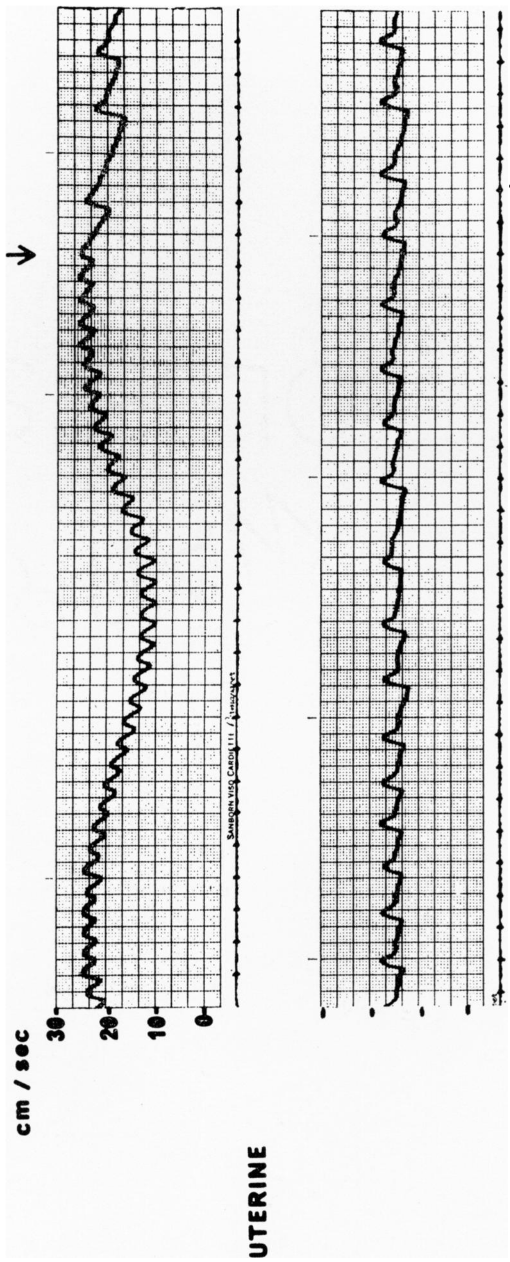
The asphyxial procedure always produced prompt and profound bradycardia. The time to onset was usually very brief, and bradycardia was well developed in less than ten seconds. This promptness in the slowing of the heart rate agrees with earlier observations of other seals.[12,13] Blood flow in the renal artery was always promptly reduced to about one tenth or less of its pre-asphyxial value, as previously observed in dived or asphyxiated dogs and harbor seals.[12] Uterine artery flow, however, was reduced only little and was sometimes unimpaired. Some momentary fluctuations in both renal and uterine artery flows occurred during asphyxial episodes ranging in duration from four to 32 minutes, but the general level of blood flows remained constant throughout. In all, 14 asphyxial experiments were performed on five animals, four of those procedures being on the animal instrumented for renal artery flow. In all experiments uterine artery flow was well maintained despite occasional fluctuations in flow and heart rate. Selected records are shown in Figure 1.

In four near-term pregant Weddell seals, records were made of maternal and fetal electrocardiograms during asphyxial experiments. The two records differed markedly in the rate of onset of bradycardia, the fetal heart rate slowing much more gradually with progressive asphyxia. Recovery was also prolonged. Figure 2 shows one typical record.

Sheep

The response to asphyxia in sheep was more varied than in seals. Bradycardia was less marked and its onset was slower and more irregular. The responses of renal and uterine arterial flow showed a consistent pattern similar to that in Weddell seals, a reduction in renal flow, and maintained uterine flow. Records were obtained in 18 experiments using five ewes. Figure 3 shows one such record.

The sheep fetus *in utero* responded to maternal asphyxia with a gradual bradycardia beginning 30 to 40 seconds after the start of apnea. The fetal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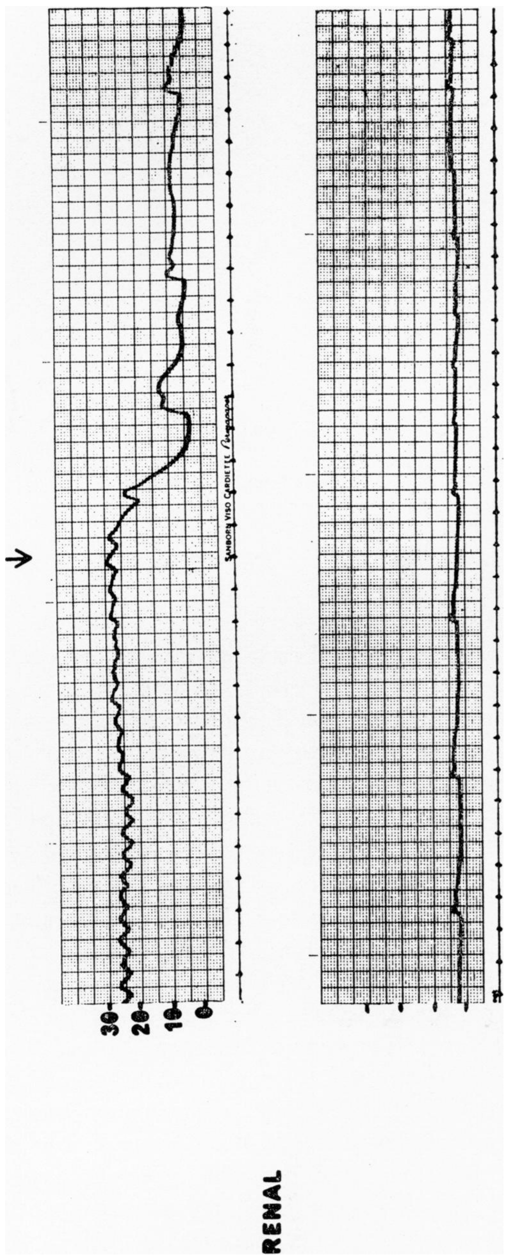

FIG. 1. Uterine and renal artery blood flow recorded separately from two pregnant Weddell seals. Arrows indicate onset of asphyxial period. Also shown are recordings of each after 5 minutes of asphyxia. Time marks indicate seconds. The difference in response in the two circulatory beds is evident.

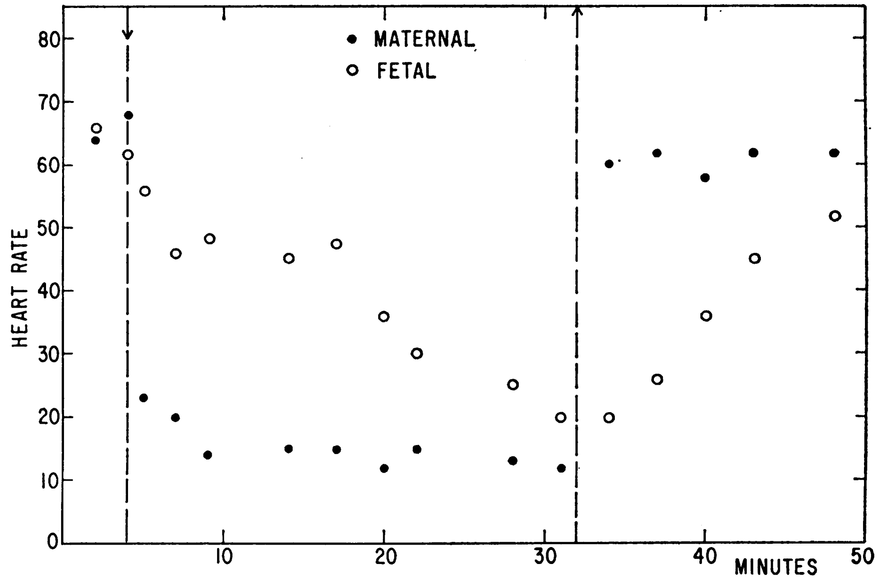

FIG. 2. Maternal and fetal heart rates in a Weddell seal. A period of asphyxia occurred between the vertical dashed lines.

responses to asphyxia of sheep and seals were therefore qualitatively similar, but the time course of these events in the sheep was considerably shorter. Fetal abdominal aorta blood flow decreased along with heart slowing. Restoration of normal heart rate and blood flow during recovery required several minutes. Eight experiments were performed in four instrumented animals. A typical blood flow recording is presented in Figure 4.

Ten experiments involving five animals were performed on term fetuses delivered by Caesarean section. Upon clamping the umbilical cord of the fetus, its heart slowed within a few seconds, as is well known from earlier descriptions.[14] Following an immediate abrupt drop in abdominal aorta blood flow as a consequence of the occlusion of a major component of outflow downstream from the transducer, there was a further decline in blood flow in the ensuing five to ten seconds. Decreased blood flow and bradycardia continued until the removal of the saline-filled glove from the head of the fetus and its subsequent first breath, when higher heart rate and elevated blood flow were promptly restored. No attempt was made to determine the maximum possible duration of this asphyxial state which would still permit recovery. Cord clamping with prevention of breathing by covering the head lasted no longer than 50 seconds. A typical record is shown in Figure 5.

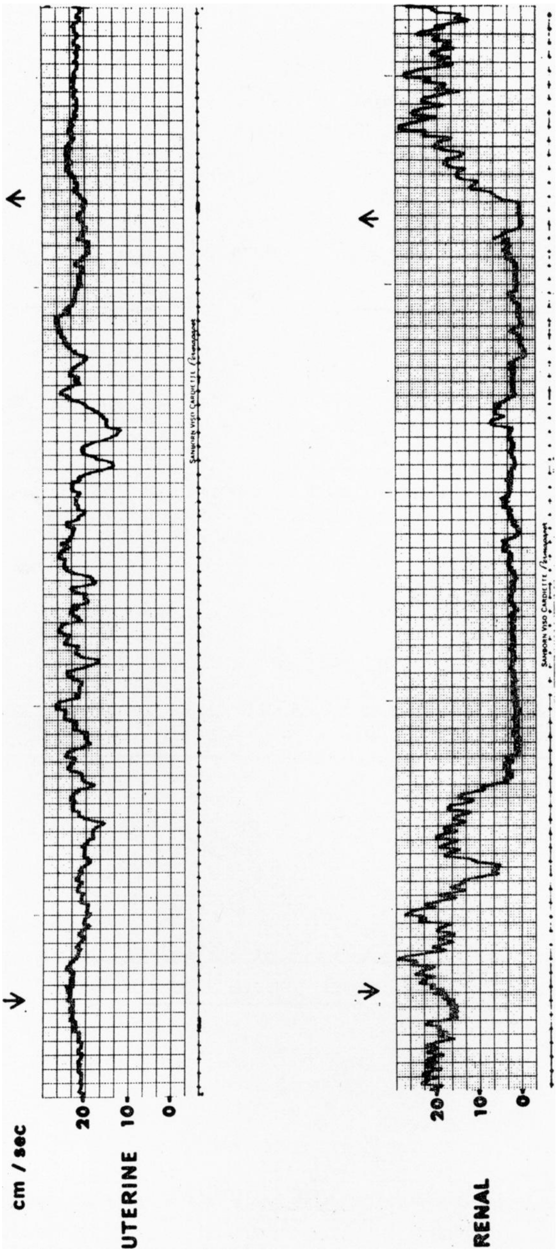

FIG. 3. Uterine and renal artery blood flow records from a pregnant ewe one week before parturition. Each record was obtained separately during experimental asphyxia lasting one minute (indicated by arrows).

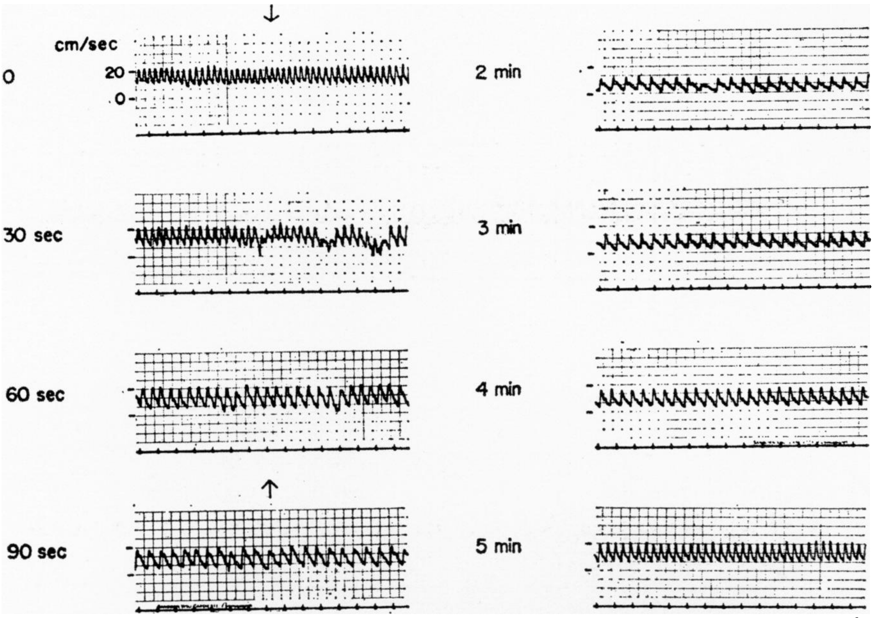

FIG. 4. Blood flow in the abdominal aorta of a near-term (138 days) fetal sheep *in utero*. The ewe was subjected to a 90-second period of asphyxia as indicated by arrows. Time marks indicate seconds. Decreasing heart rate and blood flow occurred.

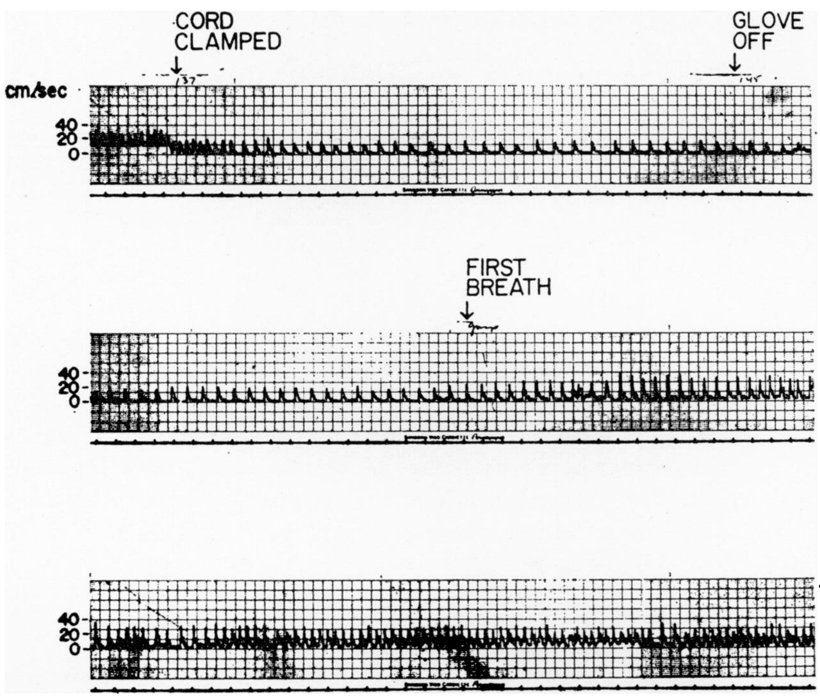

FIG. 5. Blood flow in the abdominal aorta of a mature sheep fetus delivered by Caesarean section. Breathing was prevented by covering the head with a saline-filled rubber glove. Time marks indicate seconds.

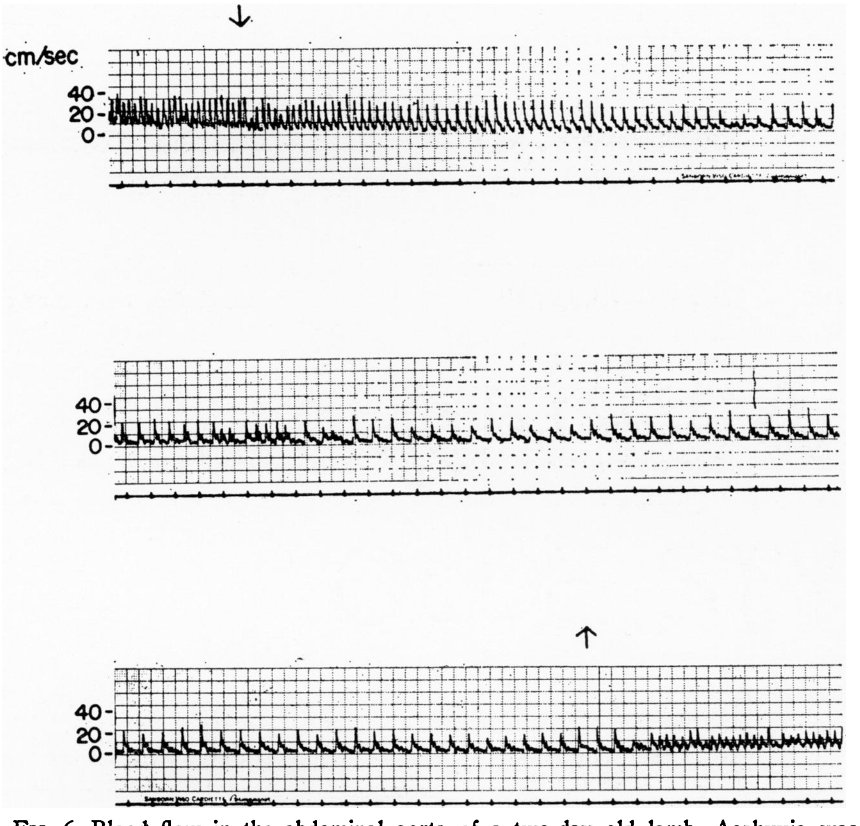

FIG. 6. Blood flow in the abdominal aorta of a two-day old lamb. Asphyxia was induced for 1.25 minutes between arrows. Time marks indicate seconds.

Four newborn lambs, two born with functioning blood flow transducers implanted on the abdominal aorta and two with similarly located transducers mounted shortly after birth, were subjected to experimental asphyxia. Their heads were immersed in water for periods up to 90 seconds. Recovery was prompt and uneventful. Twelve separate experiments were performed with lambs ranging in age from one to ten days. Bradycardia began within a few seconds of immersion, and abdominal aorta flow was simultaneously reduced (Fig. 6).

DISCUSSION

The circulatory responses to asphyxia are qualitatively similar in pregnant and fetal seals and sheep. The maintenance of uterine artery blood flow in pregnant animals of both species during asphyxia, when the circulation of most other regions was reduced, suggests that this response provides defense for the fetus by means of a continuing oxygen supply during maternal asphyxia, as would be produced by a seal's prolonged diving or a maternal accident.

A recent study of the respiratory characteristics of adult and near-term fetal blood in the Weddell seal shows that the usual shift to the left of the oxygen dissociation curve of fetal blood, indicating greater oxygen affinity, is present in this species. In contrast with human and sheep blood, however, the oxygen capacity of Weddell seal fetal blood is lower than that of the maternal blood.[15] This combination indicates that oxygenation of the fetus could be maintained during prolonged dives by a relatively small maintained blood supply to the maternal side of the placenta which would permit the fetus to draw upon oxygen stores in maternal blood.

Both the fetal and maternal circulations in sheep show some features of blood flow redistribution that could have the effect of conserving oxygen for consumption by the heart and brain or maintaining glucose transport to the brain. While the responses in sheep tend clearly in the same direction as the adjustments seen in the diving seal, as shown by this study and by the findings of Campbell, *et al.*,[8] a quantitative evaluation of these responses has not been made. In this connection it is interesting to note that Parker and Purves observed a prefertntial distribution of more oxygenated blood toward the head of the fetal lamb during maternal hypoxia.[16] The difference in oxygen contents of the ascending and descending aorta was maintained or increased during hypoxia, thus tending to enhance oxygen delivery to the coronary and cerebral circulations and contributing to the survival of heart and brain tissue during periods of interference with normal oxygenation.

Two separate mechanisms appear to be involved, one probably initiated by sensory elements located in respiratory structures, the other by chemoreceptor stimulation. The rapid onset of the circulatory changes at the beginning of apnea in seals in this study agrees with earlier findings on other seal species.[12,13,17] Neurophysiological investigations in diving ducks have shown that sensory stimulation via the trigeminal nerve was important for the reflex initiation of the circulatory responses observed.[18] In several species, including man, face immersion in water is more effective than breathholding in air in eliciting the cardiovascular responses.[13,19]

An altogether different mechanism is indicated for explanation of both the fetal responses to maternal asphyxia and the effects of umbilical cord clamping, since mechanical stimulation of the respiratory apparatus is probably not involved. A chemorecptor is likely because the responses closely resemble those of bradycardia and vasoconstriction arising from carotid body stimulation.[20] As shown by Daly and co-workers,[21,22] these primary responses are usually masked during hypoxia induced without interruption of breathing by secondary effects arising from compensatory respiratory and circulatory mechanisms. However, simple apneic asphyxia with progressively increasing hypoxia and hypercapnia produces the primary responses of bradycardia and peripheral vasoconstriction.[23] Recent experiments on fetal lambs, in which reduced femoral blood flow resulting from cord clamping was studied, indicated that aortic chemoreceptors provided the afferent signal.[24]

It seems clear that between these two examples of trigeminal and chemoreceptor reflexes there exists a wide range of responses to asphyxia, including diving as one example, in which the two mechanisms interact in varying degrees. Thus hypoxia, and to a greater extent hypercapnia, potentiate diving bradycardia in ducks.[25,26] The two mechanisms appear closely interrelated in the production of characteristic responses to the remarkable range of asphyxial episodes in a wide variety of species, from fish taken out of water[27] to the distressed human infant during birth.[28]

The analogy between diving seals and asphyxiated fetal or newborn sheep is tenable to the extent that the redistributions of cardiac output induced by interference with normal respiration represent a coordinated asphyxial defense mechanism. There are, however, clear differences in survival mechanisms. The circulatory events are more profound in seals, and seals appear to depend less on anaerobic mechanisms. Oxygen storage is clearly greater in seals, by virtue of both increased blood volume and hemoglobin concentration. Dawes suggested that the analogy between diving seals and asphyxiated fetal or newborn animals breaks down because of differences in mechanisms of survival related to dissimilarities in oxygen available from blood storage (high in seals, low in fetal lambs) and in the appearance of lactic acid in the circulating blood (mostly during post-dive recovery in seals, throughout asphyxia in fetal sheep).[1] The differences are doubtless real, and the time courses of the various observed events are sometimes widely disparate. However, it would be unwarranted to conclude that fundamental circulatory mechanisms of asphyxial defense are not the same. Whether the blood transports oxygen or glucose to the brain, the possibility of survival is enhanced.

The two species have been examined by different techniques. The lambs studied by Dawes and his colleagues were observed in asphyxia experiments continuing until the last gasping effort. If resuscitation was then promptly started, permanent brain damage apparently did not occur. Chesler and Himwich showed that the relative glycolytic activity of various parts of the dog and cat brain varied with growth.[29] The medulla of newborn animals had the highest rate, and it decreased with age while that of higher structures increased. Total brain metabolism was also less in infant than in adult animals.

Few experiments related to brain metabolism have been done in such a way as to allow direct comparison among various species of newborn animals. However, recent studies of the electroencephalograms of Weddell seals during prolonged asphyxia might be pertinent. In adult animals that were asphyxiated (or ventilated with nitrogen) beyond the point at which the EEG indicated impaired brain function (isoelectric signal), heart beat and sometimes respiratory gasps continued for some minutes even though carotid arterial blood PO_2 had been reduced to less than 10 mm Hg. Furthermore, asphyxial studies in both infant and adult seals showed that the carotid blood oxygen fell to a lower level than that required in adult terrestrial mammals to produce high amplitude slow EEG waves indicative of incipient brain metabolic disturbance.[30] This was interpreted as evidence of a specific tolerance to low cerebral oxygen reminiscent of similar resistance in fetal and newborn animals.

Seals, like fetal sheep, have an enhanced capacity for anaerobic metabolism. Lactic acid accumulates in skeletal muscle during diving.[31] Although it does not ordinarily appear in high concentration in the circulating blood until after the dive, it will do so if the seal is pressed to its diving limit. The buffer capacity of seal blood is greater than in non-diving animals,[32] and their high tolerance to carbon dioxide has been described.[33,34] Distressed newborn human infants experienced an abrupt decrease in buffer base (corresponding to increased lactic acid concentration) immediately after breathing had commenced.[35] This finding suggests a response similar to that seen in seals and other animals during recovery from a dive or asphyxia. The change in buffer base in circulating blood was observable in infants born with signs of distress, but it would probably be obscured by sustained high lactic acid concentrations in an infant asphyxiated for a period of time comparable to that of a fetal lamb in its last gasp.

While asphyxial adaptation is more noticeable in infant than in adult terrestrial animals, it improves with age in seals. Newborn elephant seals showed abrupt bradycardia upon submersion, but they were clearly stressed by more than a few minutes dive, which would be trivial for an adult.[36] Diving ability is not well developed in infant harbor seals,[37] fur seals[38] or Weddell seals.[39] Kooyman measured diving times in 104 dives by three free-swimming Weddell seal pups; the longest was five minutes, much less than the adult performance.[39] This difference in diving ability between infant and adult seals is consistent with the finding of less oxygen capacity in near-term fetal Weddell seal blood.[15] Blood volume related to body weight is probably less, too, since we have observed that the large venous reservoir of the adult inferior vena cava is undeveloped in the newborn. Direct observation of pups and mother seals clearly reveals that much of the diving technique is learned behavior.

The Weddell seal is born with a brain weighing only a little less than the adult brain.[40] With growth, the brain to body weight ratio steadily diminishes, and therefore the fraction of the total oxygen requirement needed by brain tissue also decreases. This would appear to favor the adult during long diving. The same advantage seems not to apply or to be obscured by other factors in the adult nondiving mammal, since its asphyxial tolerance is clearly inferior to that of the infant. While several asphyxial defense mechanisms have been identified, the relative significance of each to newborn and adult animals cannot be evaluated until their quantitative contributions are determined.

SUMMARY

Comparative studies of regional blood flow and heart rate have been performed in fetal and pregnant sheep and Weddell seals. The responses of these animals to experimental asphyxia were tested, and several similarities were noted. Pregnant animals reacted by reducing renal blood flow while maintaining uterine artery flow. Fetal sheep experienced reduced abdominal aorta blood flow in response to maternal asphyxia, and a similar reaction was shown in asphyxiated young lambs. Bradycardia was observed in all experiments. When maternal asphyxia occurred, fetal heart slowing and restoration of the normal rate during recovery was delayed when compared to maternal heart rates. The responses seen suggest that similar adaptive circulatory mechanisms for asphyxial survival operate in seals and sheep.

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REFERENCES

1. Dawes, G. S.: *Foetal and Neonatal Physiology*. Chicago, Year Book Medical Publishers, 1968, pp. 141-149.

2. Dawes, G. S., Mott, J. C., and Shelley, H. J.: The importance of cardiac glycogen for the maintenance of life in foetal lambs and newborn animals during anoxia. *J. Physiol. (Lond.)*, 1959, *146*, 516-538.
3. Dawes, G. S., Jacobson, H. N., Mott, J. C., Shelley, H. J., and Stafford, A.: The treatment of asphyxiated mature foetal lambs and rhesus monkeys with intravenous glucose and sodium carbonate. *J. Physiol. (Lond.)*, 1963, *169*, 167-184.
4. Kabat, H.: The greater resistance of very young animals to arrest of the brain circulation. *Amer. J. Physiol.*, 1940, *130*, 588-599.
5. Scholander, P. F.: Experimental studies on asphyxia in animals. *In*, Walker, J. and Turnbull, A. C. (eds.), *Oxygen Supply to the Foetus*. Oxford, Blackwell Scientific Publications, 1960, pp. 267-274.
6. Andersen, H. T.: Physiological adaptations in diving vertebrates. *Physiol. Rev.*, 1966, *46*, 212-243.
7. Elsner, R.: Cardiovascular adjustments to diving. *In*, Andersen, H. T. (ed.), *The Biology of Marine Mammals*. New York, Academic Press, 1969, pp. 117-145.
8. Campbell, A. G. M., Dawes, G. S., Fishman, A. P., and Hyman, A. I.: Regional redistribution of blood flow in the mature fetal lamb. *Circulat. Res.*, 1967, *21*, 229-235.
9. Kooyman, G. L.: Maximum diving capacities of the Weddell seal, *Leptonychotes weddelli. Science*, 1966, *151*, 1553-1554.
10. Elsner, R., Kooyman, G. L., and Drabek, C. M.: Diving duration in pregnant Weddell seals. *In*, M. Holdgate (ed.), *Antarctic Ecology*, in press.
11. Franklin, D. L., Schlegel, W. L., and Watson, N. W.: Ultrasonic Doppler shift blood flow meter: circuitry and practical applications. *In, Biomedical Sciences Instrumentation*. New York, Plenum Press, 1963, pp. 309-315.
12. Elsner, R., Franklin, D. L., van Citters, R. L., and Kenney, D. W.: Cardiovascular defense against asphyxia. *Science*, 1966, *153*, 941-949.
13. Scholander, P. F.: The respiratory function in diving mammals and birds. *Hvalrådets Skrifter Norske Videnskaps-Akad, Oslo*, 1940, *22*, 1-131.
14. Barcroft, J.: *Researches on Prenatal Life*. Oxford, Blackwell Scientific Publications, 1946, pp. 123-144.
15. Lenfant, C., Elsner, R., Kooyman, G. L., and Drabek, C. M.: Respiratory function of the blood of the adult and fetal Weddell seal *Leptonychotes weddelli. Amer. J. Physiol.*, 1969, *216*, 1595-1597.
16. Parker, H. R. and Purves, M. J.: Some effects of maternal hyperoxia and hypoxia on the blood gas tensions and vascular pressures in the foetal sheep. *Quart. J. exp. Physiol.*, 1967, *52*, 205-221.
17. Grinnell, S. W., Irving, L., and Scholander, P. F.: Experiments on the relation between blood flow and heart rate in the diving seal. *J. cell. comp. Physiol.*, 1942, *19*, 341-350.
18. Andersen, H. T.: The reflex nature of the physiological adjustments to diving and their afferent pathway. *Acta physiol. scand.*, 1963, *58*, 201-210.
19. Andersen, H. T.: Factors determining the circulatory adjustments to diving. I. Water immersion. *Acta physiol. scand.*, 1963, *58*, 173-185.
20. Daly, M. de B. and Scott, M. J.: The cardiovascular effects of hypoxia in the dog with special reference to the contribution of the carotid body chemoreceptor. *J. Physiol. (Lond.)*, 1964, *173*, 201-214.
21. Daly, M. de B. and Scott, M. J.: The effects of stimulation of the carotid body chemoreceptors on heart rate in the dog. *J. Physiol. (Lond.)*, 1958, *144*, 148-166.
22. Daly, M. de B. and Hazledine, J. L.: The effects of artificially induced hyperventilation on the primary cardiac reflex response to stimulation of the carotid bodies in the dog. *J. Physiol. (Lond.)*, 1963, *168*, 872-889.
23. Angell James, J. E. and Daly, M. de B.: Cardiovascular responses in apnoeic asphyxia: role of arterial chemoreceptors and the modification of their effects by a pulmonary vagal inflation reflex. *J. Physiol. (Lond.)*, 1969, *201*, 87-104.
24. Dawes, G. S., Lewis, B. V., Milligan, J. E., Roach, M. R. ,and Talner, N. S.: Vasomotor responses in the hind limbs of foetal and new-born lambs to

asphyxia and aortic chemoreceptor stimulation. *J. Physiol.* (*Lond.*), 1968, *195,* 55-81.
25. Andersen, H. T.: Factors determining the circulatory adjustments to diving. II. Asphyxia. *Acta physiol. scand.*, 1963, *58,* 186-200.
26. Feigl, E. and Folkow, B.: Cardiovascular responses in "diving" and during brain stimulation in ducks. *Acta physiol. scand.*, 1963, *57,* 99-110.
27. Leivestad, H., Andersen, H., and Scholander, P. F.: Physiological response to air exposure in codfish. *Science,* 1957, *126,* 505.
28. Hon, E. H.: Observation on "pathologic" fetal bradycardia. *Amer. J. Obstet. Gynec.*, 1959, *77,* 1084-1099.
29. Chesler, A. and Himwich, H. E.: Glycolysis in the parts of the central nervous system of cats and dogs during growth. *Amer. J. Physiol.*, 1944, *142,* 544-549.
30. Elsner, R., Shurley, J. T., Hammond, D. D., and Brooks, R.: Cerebral tolerance to hypoxemia in asphyxiated Weddell seals. *Respir. Physiol.*, in press.
31. Scholander, P. F., Irving, L., and Grinnell, S. W.: Aerobic and anaerobic changes in the seal muscles during diving. *J. biol. Chem.*, 1942, *142,* 431-440.
32. Lenfant, C.: Physiological properties of blood of marine mammals. *In,* Andersen, H. T. (ed), *The Biology of Marine Mammals.* New York, Academic Press, 1969, pp. 95-116.
33. Irving, L.: The insensitivity of diving animals to CO_2. *Amer. J. Physiol.*, 1938, *124,* 729-734.
34. Robin, E. D., Murdaugh, H. V., Jr., Pyron, W., Weiss, E., and Soteres, P.: Adaptation to diving in the harbor seal—gas exchange and ventilatory response to CO_2. *Amer. J. Physiol.*, 1963, *205,* 1175-1177.
35. James, L. S.: Acidosis of the newborn and its relation to birth asphyxia. *Acta paediat.* (*Uppsala*), 1960, *122* (Suppl.) 17-28.
36. Hammond, D. D., Elsner, R., Simison, G., and Hubbard, R.: Submersion bradycardia in the newborn elephant seal *Mirounga angustirostris. Amer. J. Physiol.*, 1969, *216,* 220-222.
37. Harrison, R. J. and Tomlinson, J. D. W.: Normal and experimental diving in the common seal (*Phoca vitulina*). *Mammalia,* 1960, *24,* 386-399.
38. Irving, L., Peyton, L. J., Bahn, C. H., and Peterson, R. S.: Action of the heart and breathing during development of fur seals. *Physiol. Zool.*, 1963, *36,* 1-20.
39. Kooyman, G. L.: An analysis of some behavioral and physiological characteristics related to diving in the Weddell seal. *In, Biology of the Antarctic Seas,* edited by Schmitt, W. L. and Llano, G. A. Vol. 2, Antarctic Research Series, Washington, American Geophysical Union, 1968, pp. 227-261.
40. Elsner, R. and Hammond, D. D.: Unpublished observations.