Response of the Fetal Mesenteric Microvascular System to Maternal Hypoxia[1] (34277)

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(Introduced by R. C. Crafts)

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Several studies have been reported on general cardiovascular responses of the fetus to maternal hypoxia or anoxia. These were reviewed recently by Dawes (1) and Rudolph and Heymann (2). The specific response of the fetal microvascular system to maternal hypoxia, however, has not been reported due, in part, to the difficulty involved in examining these vessels directly *in vivo* with the light microscope while maintaining homeostasis. This poor understanding of the microvascular system has prompted a series of studies of these vessels *in vivo* in rabbit fetuses with their placental circulations intact (3–6). The present paper reports the effect of maternal hypoxia on the fetal mesenteric microvascular system.

Materials and Methods. The mesenteries of 50 fetal and 15 adult pregnant rabbits (New Zealand albino) were studied. Fetal preparations and adult preparations were studied independently since technical complications did not permit simultaneous microscopic observations of fetal and adult mesenteries. In both preparations pregnant rabbits were anesthetized with ethyl carbamate (Urethane, 1.5 g/kg). To study the fetal mesentery a fetus was exteriorized with its placental circulation intact on various days of gestation between days 25 and 32 (av gestation in the rabbit is 32 days) and the fetal mesentery was exposed surgically. Homeostasis was maintained by constant irrigation with Ringer's solution of the surface of the mesentery as well as the fetal body surface which was covered with gauze sponges. The temperature of the Ringer's was maintained at the maternal body temperature by regulating heaters (3–6). In addition, the ambient air surrounding the fetus was maintained at 37.5° by a Sage "air curtain" with its controlling thermister probe placed on the surface of the fetus. To study the mesentery of the pregnant adult rabbit, the uterus was displaced and a loop of bowel was exposed. Homeostasis was maintained as in the fetus.

Observations of the mesentery of the fetus or of the pregnant adult were accomplished by transillumination of the tissue with light conducted to the mesentery by a hollow, fused quartz-rod (7) and examination with a Leitz stereo-binocular microscope equipped with 2×, 4×, 8×, and 12× objectives and 12.5× and 18× oculars. Using these optics magnifications of 25–216× were obtained. Alternatively, a modified Leitz compound monocular microscope was used equipped with 10×, 22×, 50×, and 90× water immersion objectives and a 10× ocular to provide magnifications to 900×. Measurements of the internal diameters of vessels were secured with a calibrated micrometer disc in the oculars.

To study the response to hypoxia of the mesenteric microvasculature of the fetus and pregnant adult, the mother received a mixture of 8% O_2/92% N_2 gas for 30 min by means of a closed circuit anesthetic machine. Then the low oxygen mixture was removed and the animal was allowed to recover breathing room air. This procedure also was repeated in fetuses and mothers to whose mesenteries an alpha-adrenergic blocking agent, phentolamine (50 μg), or a beta-adrenergic blocking agent, propranolol (50 μg), had been applied topically. Maternal

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and fetal blood pH, pO_2 and pCO_2 were monitored using an ultramicro blood gas analyzer (Instrumentation Laboratories, model 123-S1, 125A).

The effect of catecholamines on the mesenteric microvasculature of the fetus and adult was tested by local, topical application of epinephrine (10 μg), and norepinephrine (10 μg) both before and after application of phentolamine or propranolol.

The responses of the fetal mesenteric microvasculature to hypoxia and subsequent recovery were recorded cinéphotomicrographically and were compared with those in the maternal mesenteric microvasculature.

Results. The responses of the fetal mesenteric microvasculature to acute hypoxia in the mother were vasoconstriction, reduced flow in large arterioles and venules (100–300 μ i.d.), severely reduced flow in small arterioles and venules (less than 100 μ i.d.), and elimination of flow in most capillaries. These responses occurred within 30 min after the administration of 8% O_2 was initiated. Recovery occurred within 20 min after the removal of the low oxygen mixture (Fig. 1). Similar responses were observed in the maternal mesenteric microvasculature but the responses were seen within 20 min with a lag in the initiation of the vasoconstriction and with recovery within 5–10 min (Fig. 1). During recovery vessel diameter was restored in parallel with blood pO_2 while pCO_2 still was elevated and pH depressed.

The above responses could be mimicked by local, topical application of epinephrine or norepinephrine. Local topical application of phentolamine blocked the above vasoconstrictive responses caused by hypoxia (Fig. 1), epinepherine, or norepinephrine in both the fetal and maternal vessels and occasionally resulted in a slight dilatation of these vessels. Propranolol, however, failed to block the vasoconstrictive response to hypoxia. Acute maternal hypoxia did not induce tissue edema nor did it lead to intravascular erythrocyte aggregation and sludging in the vessels examined.

Discussion. These data illustrate that the response of the fetal mesenteric microvascular system to hypoxia is vasoconstriction and suggests that this response is mediated by an oxygen dependant, alpha-adrenergic mechanism since: (i) the response could be mimicked by the administration of epinephrine or norepinephrine and could be blocked by an alpha-adrenergic blocking agent, phentolamine, but could not be blocked by a beta-adrenergic blocking agent, propranolol; and (ii) vessel diameter returned in parallel with blood pO_2 while blood pCO_2 remained elevated and blood pH depressed. Thus, it would seem that recovery following hypoxia in the fetal microvasculature and reestablishment of blood flow through capillaries of the mesenteric tissue is not so much dependant on the blood acid–base balance and pCO_2 as it is upon blood pO_2, a finding that is in agreement with the results of Godfrey (8).

At this time, however, it is not clear whether the vasoconstriction is due to reflex neural mechanisms initiated by chemoreceptors, is due to humoral mechanisms, e.g., elaboration of epinephrine from the suprarenal, or is possibly a direct effect of hypoxia on the vessel wall. While the existence of functional chemoreceptors and autonomic innervation in the fetus is not clear (1, 2, 9–13), several studies suggest the importance of catecholamine release from the suprarenal during the last half of gestation in the response of the fetus to stress (1, 2, 14). Unfortunately, there is little or no information concerning the sensitivity of the fetal systemic vascular wall to varying concentrations of oxygen in the blood. Studies on isolated adult vessels, however, indicate that hypoxia induces vasodilatation, except in the lung where vasoconstriction is the result (15). While vasoconstriction of pulmonary vessels in response to hypoxia also has been demonstrated to be a direct, local effect in the fetus (1), there is little information concerning such direct action in the fetal systemic vessels. In addition, the relative sensitivities of the fetal systemic vessels compared with the adult to varied oxygen concentrations have not been reported.

In this study the data suggest that the response of the maternal and fetal vessels to maternal hypoxia are equivalent. Both maternal and fetal arterioles constricted approx-

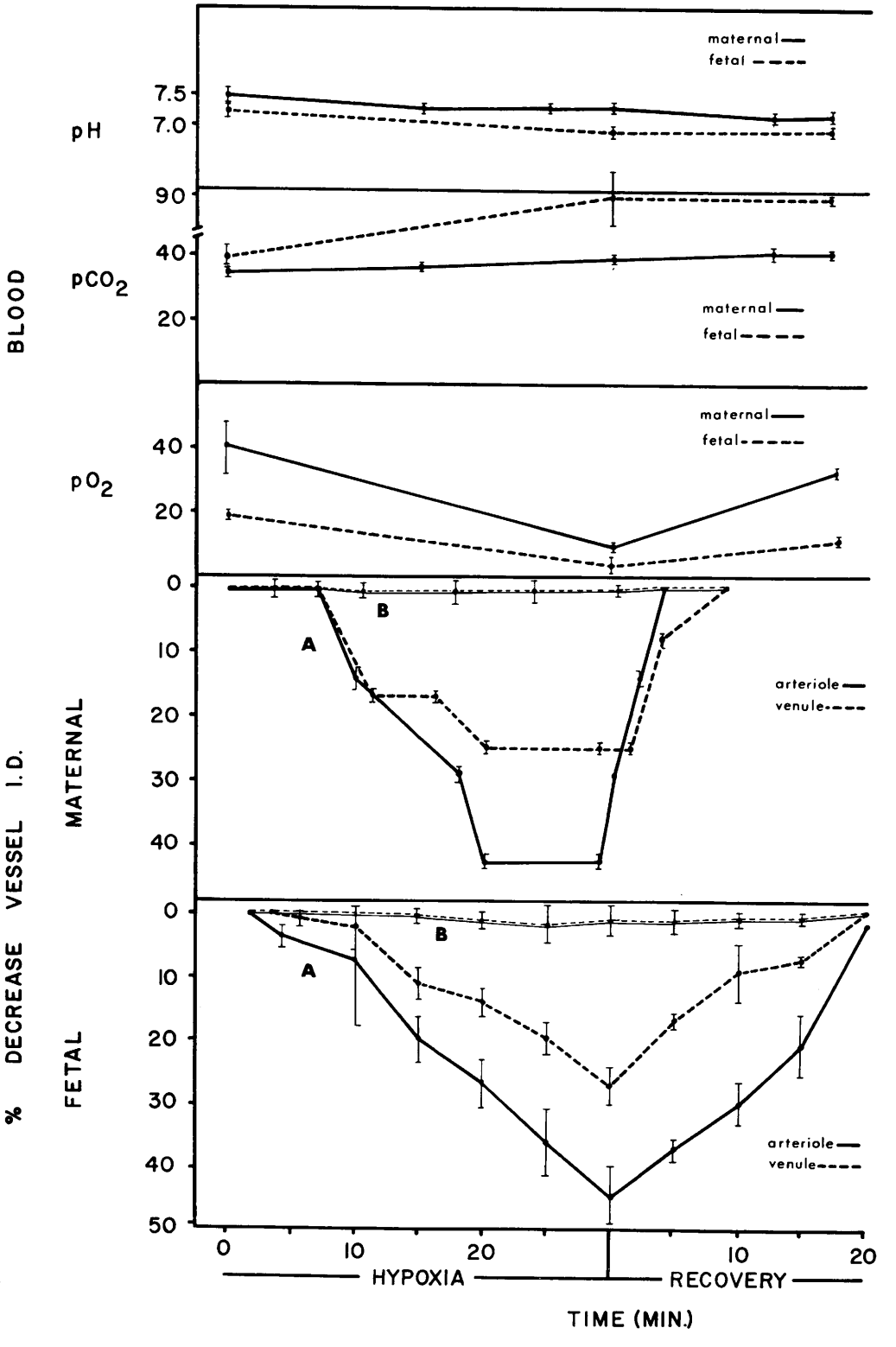
BLOOD
pH
7.5
7.0
maternal
fetal
90
40
20
pCO2
maternal
fetal
40
20
0
pO2
maternal
fetal
% DECREASE VESSEL I.D.
MATERNAL
0
10
20
30
40
B
A
arteriole
venule
FETAL
0
10
20
30
40
50
B
A
arteriole
venule
0
10
20
10
20
HYPOXIA
RECOVERY
TIME (MIN.)

FIG. 1. Changes (± the standard error of the mean) in the internal diameters of vessels in fetal and maternal mesenteric microvasculature, and changes in pH, pO_2, and pCO_2 of the fetal and maternal blood, during hypoxia and recovery in anesthetized rabbits: A, normal response to hypoxia and following administration of propranolol; B, response to hypoxia after administration of phentolamine.

imately 45% while venules constricted approximately 25%. The smaller degree of venular constriction suggests that these vessels may have less functional innervation, may be less sensitive to catcholamines released from the suprarenal, or may be less sensitive to low oxygen saturation of the blood. The most probable explanation, however, is that these vessels contain considerably less smooth muscle in their walls than do their companion arterioles and are less capable of vasoconstriction.

Summary. The effect of maternal hypoxia on the microvascular system of fetal and pregnant adult rabbits was studied. The response of the fetal mesenteric microvasculature to hypoxia was vasoconstriction, reduced flow in the large arterioles and venules, and severely reduced flow in most capillaries. This response occurred within 30 min after initiation of 8% O_2; recovery occurred within 20 min after removal of the low oxygen mixture. Similar findings were obtained in the maternal mesenteric microvasculature but the responses were more rapid, occurring within 20 min, with recovery within 5–10 min. The responses appeared to be mediated by an oxygen dependant, alpha-adrenergic mechanism since, during recovery, flow and vascular diameter were restored in parallel with the blood pO_2 even though blood pH still was depressed and pCO_2 was elevated, and since the vasoconstrictive response could be blocked by phentolamine but not by propranolol.

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