Effects of Hypothermia on Uterine Circulation and on the Fetus.* (27243)

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We showed previously(1) that changes in systemic and regional blood flows and vascular resistances induced by hypothermia depend on the presence or absence of shivering. When shivering is permitted, renal and carotid flows fall despite unchanged cardiac output. Femoral flow rises because of increased muscular activities. If shivering is abolished, cardiac output and renal and femoral flows decrease. Carotid flow increases probably because of high pCO_2.

Since hypothermia has been used in pregnant women as a treatment for different diseases(2,3), the present study was undertaken to investigate its effects on the circulation of the pregnant uterus and on fetal survival.

Material and method. Ten pregnant bitches (15-25 kg) were studied in the latter part of gestation. Five were anesthetized with Sernyl (2 mg/kg) to maintain intact shivering mechanisms, and in the other 5 pentobarbital was used in doses to keep deep narcosis and abolish shivering. The technics of measuring uterine, carotid and femoral blood flows and arterial pressure and of monitoring skin, rectal and blood temperatures were the same as reported elsewhere(1). One uterine horn was exposed and a thermistor was passed into one amniotic cavity through a purse string suture made in the uterine muscle. Fetal temperature was recorded with another thermistor attached to the fetus through another purse string suture. In some bitches, intra-amniotic pressure was measured with a catheter inserted into the amniotic sac and connected to a Statham strain gauge. The abdomen was closed leaving the lead wires of the flowmeters and of the thermistors and the pressure catheter emerging from an edge of the incision. Control recordings of flow, pressures and temperatures were taken for one hour. Thereafter, cooling and rewarming of the bitch were carried out as previously described(1). In some animals, the puppies were delivered at the end of the cooling period, while in others they were removed after rewarming was completed.

Results. Fig. 1-3 illustrate the changes in temperatures, pulse, respiration, arterial pressure and uterine blood flow observed in a representative example of a shivering bitch anesthetized with Sernyl. Table I summarizes the data on uterine blood flow and vascular resistance. Temperature of the fetus was the same as that of the amniotic fluid in the control, cooling and rewarming periods, and changed in a pattern similar to that of the rectal temperature of the mother (Fig. 1). Pulse rate of the mother fell markedly during cooling and rose moderately during rewarming, whereas respiration changed irregularly (Fig. 2). Blood pressure rose initially during cooling but returned to control thereafter (Fig. 3). Uterine blood flow fell rapidly and markedly during cooling and re-

TABLE I. Mean Values of Uterine Blood Flow and Vascular Resistance during Hypothermia. Combined standard error of mean in control period is given.

Temp., °C	Uterine flow, ml/min./kg	Uterine vascular resistance, mmHg/ml/min./kg
	A—Shivering animals	
Control	7.0 ±.35	15
37	6.2	27
34	5.1	34
30	3.5	42
28	3.0	40
	B—Nonshivering animals	
Control	6.1 ±.45	12
37	4.2	20
34	3.8	24
30	2.8	30
28	2.2	34

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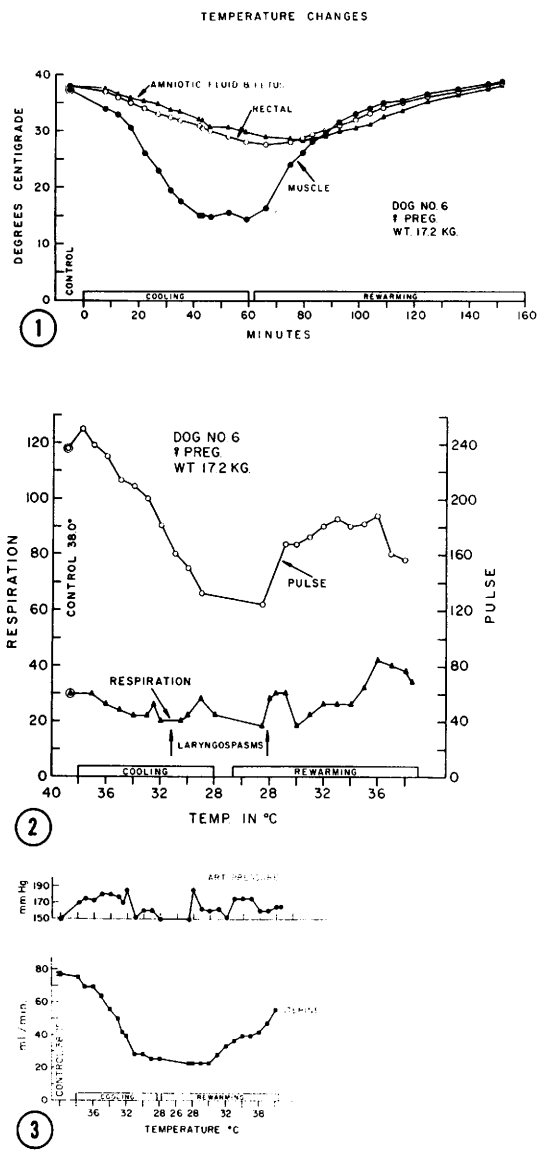

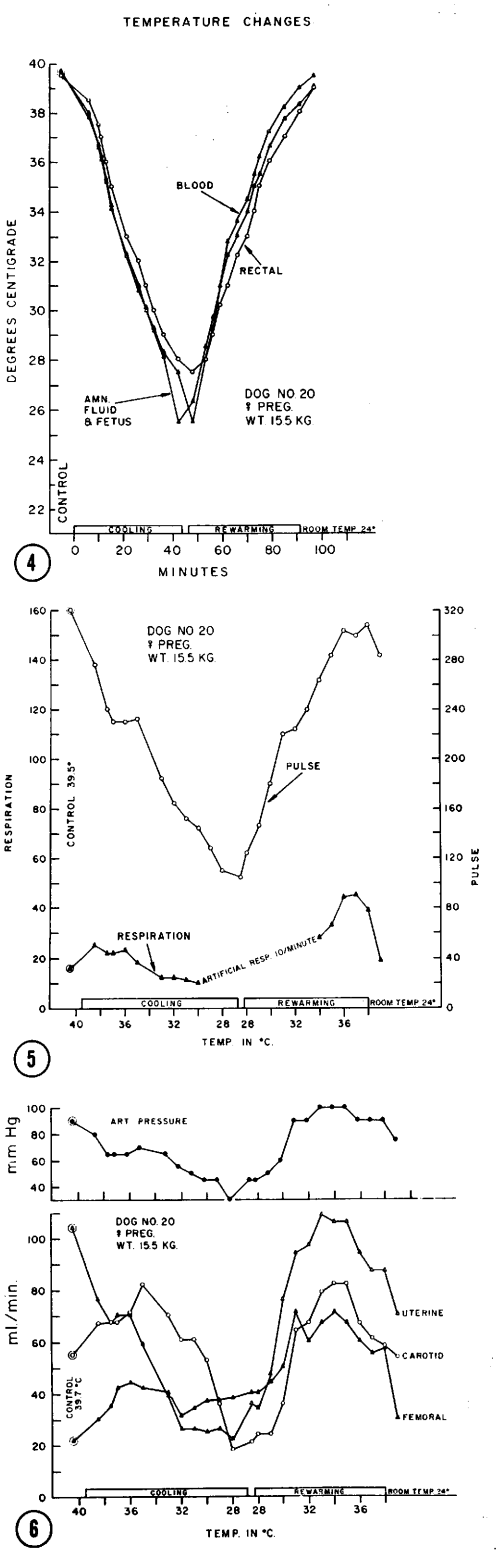

FIG. 1. Temperature changes of mother and fetus in a shivering animal.

FIG. 2. Changes in pulse rate and respiration in a shivering animal.

FIG. 3. Changes in blood pressure and uterine blood flow in a shivering animal.

FIG. 4. Fetal and maternal temperatures in a nonshivering animal.

FIG. 5. Pulse and respiration in a nonshivering animal.

FIG. 6. Changes in arterial pressure and uterine blood flow in a nonshivering animal. Carotid and femoral flows are given for comparison.

turned slowly toward normal during rewarming (Fig. 3, Table I). Uterine vascular resistance increased strikingly during cooling and decreased during rewarming (Table I). Intrauterine pressure rose from 5 mm Hg to 15 during cooling and returned to control during rewarming.

Fig. 4-6 illustrate a typical example of a nonshivering bitch anesthetized with pentobarbital. Blood and rectal temperatures of the mother fell more rapidly than in the shivering bitch, a finding consistent with the previous data(1). Fetal and amniotic fluid temperatures paralleled those of maternal blood (Fig. 4). Changes in pulse rate and respiration during cooling and rewarming were more marked than those of the shivering animal (Fig. 5). Arterial pressure and uterine blood flow fell steadily during cooling, the latter reaching values which were 80% less than control. During rewarming, arterial pressure and uterine blood flow returned slowly to control values (Fig. 6, Table I). Intrauterine pressure and uterine vascular resistance rose during cooling and fell during rewarming. Carotid and femoral flows changed in a manner similar to that described earlier(1).

In 6 bitches, the puppies were delivered at the end of the rewarming period. All had a good muscular tone and pink mucosas and breathed spontaneously after cutting the cord. In the remaining 4, the puppies were delivered at the end of the cooling period. The uterus was tense and in a state of contraction in contrast to the soft uterus seen in the animals which were rewarmed. The puppies had a good color and muscular tone but did not breathe until 3-4 minutes after cord section. Their survival rate, however, was the same as that of the group delivered after rewarming.

Discussion. The present studies show that blood flow to the pregnant uterus decreases markedly during hypothermia regardless of whether the animal is shivering. This uterine response is similar to that of the kidney and differs from that of the skeletal muscles(1). Since in the shivering animal the fall in uterine blood flow is independent of the changes in cardiac output(1), an active constriction of the uterine vessels must occur during hypothermia. This constriction is probably caused by contraction of the uterine muscle around the vessels and hence by increase in the intramural resistance. This hypothesis is supported by the rise in intrauterine pressure and by the finding of a tense and contracted uterus during cooling. Whether the uterine contraction is caused by neurogenic reflex elicited by cooling or by stimulation of oxytocin release cannot be stated. In the nonshivering animal, the fall in cardiac output probably accounts for the decrement in uterine flow. Despite the marked fall in uterine blood flow and its effect on oxygen transfer across the placenta, the fetus does not seem to be affected since the survival rate of the 2 groups was the same. The fact that the onset of breathing was delayed in the puppies delivered during cooling suggests that the respiratory center was depressed by cold without any detriment to the organism. This is in agreement with data obtained from human subjects(3). Evidently, the rapid fall in temperature of the fetus must have contributed to its tolerating any hypoxia which might have occurred during the period of uterine ischemia. The fall in fetal temperature is brought about by the rapid heat exchange between fetal and maternal circulation in the placenta and also by the fall in amniotic fluid temperature. The alteration in temperature of the amniotic fluid must be the result of heat exchange between uterine circulation and amniotic sac, since the temperatures in these 2 compartments changed in similar fashion. Therefore, the fetus *in utero* is protected against the effects of hypothermia in the mother by lowering its temperature, decreasing thereby its metabolic activities and its need for oxygen.

Summary. 1. The effects of immersion hypothermia on uterine circulation and on the fetus were investigated in shivering and nonshivering dogs. 2. Uterine blood flow decreased markedly in both groups and the fall was associated with a marked increase in uterine vascular resistance. In the shivering dogs, contraction of the uterine muscle and increase in intramural resistance are probably

responsible for the fall in uterine flow. 3. Despite the uterine ischemia, fetal survival is not affected because fetal temperature falls to the same extent as that of the mother. Hypothermia of the fetus *in utero* probably increases its tolerance to hypoxia.

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Release of Norepinephrine from the Heart by Vasoactive Amines. (27244)

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Although it has been suggested that the action of some sympathomimetic amines is mediated by release of endogenous norepinephrine (NE) from adrenergic nerve endings (1,2), little direct evidence supports this view. *In vitro*, tyramine has been shown to increase the rate of release of NE from isolated granules of splenic nerve and adrenal medulla(3,4). Stjarne(5) utilizing a bioassay technic, observed an increase of a pressor substance in the splenic vein effluent following administration of tyramine. On the other hand, no reduction in NE content of guinea pig hearts was observed after prolonged perfusion with tyramine(6) and no increase in NE content of arterial blood of intact animals was detected after injection of tyramine(7, 8). Accordingly, it was suggested that the action of this amine is a direct one and that NE merely plays a facilitating role(6). Therefore, the purpose of the present study was to determine whether, in the intact anesthetized dog, a number of vasoactive amines actually release NE from the heart by direct measurement of catecholamines in coronary sinus blood. The influence of one of these, tyramine, on concentration of NE in cardiac tissue was also determined.

Methods. Fourteen mongrel dogs weighing 18 to 30 kg were lightly anesthetized with morphine (2 mg/kg subcutaneously) and a chloralose-urethane mixture given intravenously. The coronary sinus was catheterized under fluoroscopic control. Blood samples of 30 ml were withdrawn simultaneously from the femoral artery and coronary sinus and were replaced with fresh donor blood which had been mixed with the experimental dog's blood prior to study. In any one experiment one to 4 sympathomimetic amines were administered. After the control samples were obtained, the amine was injected, and at the time of maximal arterial pressure response blood samples were taken from the coronary sinus and femoral artery. Thirty minutes after injection, when arterial pressure had returned to control levels, blood samples were again obtained and another amine injected. In 5 additional open-chest dogs tyramine was infused continuously for one hour at a rate of 200 μg/kg/min., while arterial pressure was recorded continuously. The right atrial appendage was biopsied prior to the infusion and the left atrial appendage at the end of infusion. Control studies were carried out identically in 4 dogs which received saline infusions, and both appendages were biopsied simultaneously in another 5 dogs which had not received vasoactive amines.

Plasma NE was isolated using alumina columns and oxidized to the trihydroxyindole (9,10). Fluorescence measurements were made in an Aminco-Bowman spectrophotofluorimeter, differentiating NE from epinephrine by the spectral characteristics of each (10). NE content of atrial appendage was purified and assayed from a trichloroacetic acid extract(9).