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The Effects of Methoxamine and Ephedrine in Normotensive Pregnant Primates

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Uterine blood flow, maternal hemodynamics, and fetal and maternal blood gases were measured before, during and after the administration of methoxamine and ephedrine to pregnant monkeys during normotension under nitrous oxide–oxygen analgesia. Methoxamine increased maternal blood pressure and total peripheral vascular resistance and decreased cardiac output, maternal heart rate, and uterine blood flow. Ephedrine increased maternal heart rate, but did not alter blood pressure, total peripheral vascular resistance, cardiac output, or uterine blood flow. While the fetus was unaffected by ephedrine, it manifested signs of asphyxia with methoxamine. After the vasopressors were discontinued uterine blood flow decreased with ephedrine and increased with methoxamine. (Key words: Uterine blood flow; Primates; Pregnancy; Methoxamine; Ephedrine; Vasopressors; Hemodynamics.)

In efforts to protect the circulatory exchange between mother and fetus by the use of vasopressors, attitudes have swung from one extreme to the other. Boba *et al.*[1] and Gabel and associates[2] found that methoxamine (Vasoxyl) and neosynephrine worsened fetal hypoxia and fetal bradycardia during hemorrhage in pregnant dogs. Greiss and associates[3,4] studied the effects of several vasopressors on uterine blood flow in sheep with electromagnetic flowmeters. Although fetal responses were not recorded in the latter study, vasopressors in general were declared dangerous because they caused uterine vasoconstriction, with consequent decrease in uterine blood flow. In support of these findings, compromise in human fetuses was suggested by the finding of fetal bradycardia after methoxamine administration.[5] These studies led to the widespread teaching that vasopressors should be given to pregnant patients only when the life of the mother was in jeopardy.[6] However, Shnider *et al.* examined fetal blood gases in ewes during the treatment of spinal hypotension with ephedrine[7] and methoxamine.[8] They found ephedrine restored fetal blood gases towards normal but methoxamine aggravated the fetal deterioration in blood gases.

Spinal anesthesia is popular in obstetrics, and hypotension remains a common complication. Uterine displacement, rapid hydration with intravenous solutions, and even prophylactic ephedrine have been recommended when high spinal block is used.[9] Because of this endorsement of a prophylactic vasopressor, we wished to examine the effects of pressors on the placental circulation in the absence of spinal hypotension. The present study was designed to compare the effects of two of the pressors most commonly used, methoxamine and ephedrine, on the maternal cardiovascular system, uterine blood flow, fetal circulation, and fetal respiratory gases in pregnant primates during normotension.

Materials and Methods

Three baboons with an average weight of 18.0 kg and 13 macaques with an average weight of 6.8 kg were selected for study at 141–160 days of gestation. Since normal gestation is 174 days, this corresponds to the last

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trimester in human pregnancy. The animals were fasted for 12 hours before the study. They were premedicated with an intramuscular injection of phencyclidine (Sernylan, Parke Davis), 0.8 mg/kg, and atropine, 0.1 mg, 30 minutes before induction of anesthesia. Anesthesia was induced with 50 mg thiopental (Pentothal, Abbott) and maintained with a succinylcholine infusion and 60–75 per cent nitrous oxide in oxygen after intubation of the trachea. Respiration was controlled with an Ohio constant-volume ventilator. Rectal temperature was monitored with a Yellow Springs thermistor and maintained at 37–38 C with a heating pad (Gormann-Rupp). The animal was placed in the left semilateral position to avoid compression of the vena cava by the gravid uterus.

Catheters were inserted into both femoral arteries and a femoral vein and advanced into the aorta and vena cava, respectively, above the point of uterine compression.

Halothane in concentrations of 0.7 to 1 per cent was administered for uterine relaxation during uterine manipulations. A small incision was made in the uterus at a site free of placenta and directly over a fetal leg. The leg was delivered through this small hysterotomy incision, with care being taken not to lose excessive amounts of amniotic fluid. Catheters (Clay Adams, P.E. 10) were inserted into a fetal femoral artery and vein. The fetal leg was replaced in its normal intrauterine position and warm saline solution was substituted for the amniotic fluid lost during the procedure. The uterus was then closed with a purse-string suture.

Catheters were also inserted into the right and left utero-ovarian veins via uterine venous tributaries. After this was done, halothane was rapidly eliminated. The abdomen was closed, and an hour was allowed for clinical evidence of halothane anesthesia to disappear. Blood loss was estimated and replaced with fresh heparinized primate blood.

Maternal arterial and central venous pressures and fetal arterial pressures were measured with Statham pressure transducers and recorded on a GME recorder. Maternal cardiac output was measured by the indicator dilution technique using indocyanine green dye and a continuously recording densitometer. Peripheral vascular resistance (TPR) was calculated in dynes-sec cm^{-5} from the formula:

$$\text{TPR (dynes-sec cm}^{-5}) = \frac{\text{mean arterial pressure (mm Hg)} - \text{mean venous pressure (mm Hg)}}{\text{Cardiac output (ml/sec)}} \times 1332$$

Uterine blood flow was measured by the steady-state equilibrium technique.[10, 11] The indicator, tritiated water, was infused at a constant rate into the fetal femoral vein for at least 50 minutes prior to the first blood flow determinations to insure a constant rate of transfer into maternal tissues. With knowledge of the rate of infusion and the amounts of indicator being retained in fetal tissues and in the uterus, the rate of passage of tritiated water across the placenta was estimated. Uterine blood flow was calculated from the rate of passage of the tritiated water and the venous–arterial concentration difference across the placenta.

Blood samples were drawn immediately following a uterine blood flow estimation and submitted for pH, P_{O_2}, P_{CO_2}, and base excess determination by the Astrup technique at 38 C. Hemoglobin values of these samples were also determined. Per cent saturation and oxygen content were calculated from oxygen dissociation curves for macaques[12] and baboons.[13] Uterine oxygen consumption was calculated as arteriovenous oxygen difference multiplied by uterine blood flow rate.

Samples were taken and measurements made during an initial control period, a test period, and a second control period. For a test period, either methoxamine, 0.3 per cent, or ephedrine, 0.05 per cent, was infused using a Harvard pump adjusted to a rate which produced either a 20 per cent increase in mean maternal arterial pressure or a 20 per cent change in maternal heart rate. The nine animals given methoxamine received an average dose of 1.3 mg/kg over 57 minutes. The second control period was begun after the heart rate and blood pressure had returned to the first control levels. The average time for this to occur was 45 minutes.

Our results were analyzed by Student's *t*

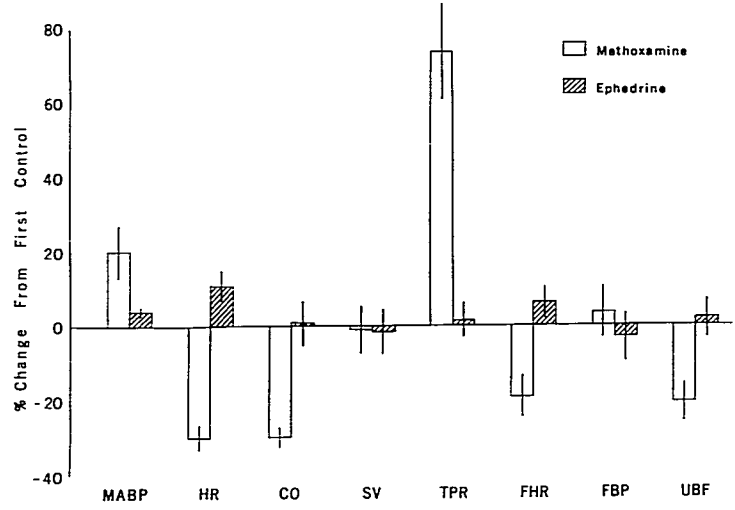

FIG. 1. Per cent changes in maternal and fetal hemodynamics (mean ± SE). MABP = mean maternal arterial blood pressure (9M, 7E). HR = heart rate (9M, 7E). CO = cardiac output (9M, 7E). SV = stroke volume (9M, 7E). TPR = total peripheral resistance (9M, 7E). FHR = fetal heart rate (9M, 6E). FBP = fetal arterial blood pressure (8M, 6E). UBF = uterine blood flow (6M, 6E). Number in parentheses indicates the number of animals included in a methoxamine (M) or ephedrine (E) treatment.

test and $P < 0.05$ was taken as significant. The data from the three baboons, all in the methoxamine-treated group, were combined with those from the macaques. Where body weight was considered a critical factor, *e.g.*, cardiac output, total peripheral resistance, the actual value was converted to per cent change from the first control value (fig. 1). When this maneuver changed the significance of an observation, it is mentioned under "Results."

Results

Maternal hemodynamic data are presented in table 1. In the mother, methoxamine increased arterial blood pressure, decreased heart rate, and increased total peripheral vascular resistance. Cardiac output declined, though not significantly. This decline does become significant ($P < 0.001$) when analyzed as per cent change from the first control value. Stroke volume changes were not significant. Ephedrine, on the other hand, increased heart rate without producing any other significant hemodynamic changes (table 1).

In general, the mother's respiratory gases remained stable (table 2). Maternal metabolic acidosis progressed with time and was reflected in the fetus.

Mean uterine blood flows decreased during administration of methoxamine and remained relatively unchanged with ephedrine (table 3). After methoxamine was discontinued, there was a suggestion of a rebound in uterine blood flow. In comparison, the animals previously treated with ephedrine had significant decreases in uterine blood flow during the second control period. There were no significant changes in A-V_{O_2} difference across the uterus or in the oxygen consumption of the uterus

TABLE 1. Maternal Hemodynamics during Infusion of Methoxamine and Ephedrine (Mean ± SD)

	Number of Subjects and Treatment	Control I	Test	Control II
Mean arterial blood pressure (mm Hg)	9, methoxamine 7, ephedrine	107.5 ± 14.2 120.9 ± 16.6	127.2 ± 18.6* 123.9 ± 16.4	110.6 ± 14.9 121.7 ± 17.3
Heart rate (beats/min)	9, methoxamine 7, ephedrine	148.2 ± 26.3 168.7 ± 4.6	103.9 ± 21.0§ 186.7 ± 16.5‡	142.7 ± 23.2 178.5 ± 13.9
Cardiac output (l/min)	9, methoxamine 7, ephedrine	1.64 ± 0.80 1.07 ± 0.22	1.16 ± 0.60 1.06 ± 0.21	1.47 ± .90 1.06 ± .17
Total peripheral resistance (dynes/sec/cm^{-5})	9, methoxamine 7, ephedrine	5,984.8 ± 3,012 8,955 ± 1,509	10,151.1 ± 4,510.2§ 8,997 ± 1,631	7,403.8 ± 3,504.1 8,702 ± 1,535
Stroke volume (ml)	9, methoxamine 7, ephedrine	11.6 ± 7.5 7.7 ± 4.2	12.0 ± 9.4 7.8 ± 5.5	10.6 ± 8.7† 7.4 ± 4.1

* Versus control I and control II, $P < 0.01$.
† Versus test, $P < 0.01$.
‡ Versus control I, $P < 0.005$.
§ Versus control I and control II, $P < 0.001$.

TABLE 2. Maternal Respiratory Gases during Infusion of Methoxamine and Ephedrine (Mean ± SD)

	Number of Subjects and Treatment	Control I	Test	Control II
P_{O_2} (mm Hg)	9, methoxamine 7, ephedrine	126.3 ± 23.3 113.9 ± 26.7	111.4 ± 25.8 117.3 ± 22.1	116.0 ± 29.8 110.0 ± 23
*p*H	9, methoxamine 7, ephedrine	7.412 ± 0.054 7.397 ± 0.118	7.374 ± 0.062 7.392 ± 0.094	7.359 ± 0.068 7.361 ± 0.070
P_{CO_2} (mm Hg)	9, methoxamine 7, ephedrine	30.6 ± 5.4 30.4 ± 6.4	31.3 ± 4.9 27.3 ± 6.0*	32.7 ± 7.7 27.5 ± 5.2
Base excess (mEq/l)	9, methoxamine 7, ephedrine	−4.1 ± 3.1 −5.5 ± 2.5	−6.0 ± 2.9 −7.3 ± 1.4*	−6.5 ± 2.8 −9.0 ± 2.3†

* Compared with control I, $P < 0.02$.
† Compared with test, $P < 0.005$.

and its contents during administration of either pressor.

Fetal blood pressure and heart rate changes are summarized in table 4. A significant decrease in fetal heart rate occurred with methoxamine, while heart rate tended to increase with ephedrine.

The fetuses in the methoxamine-treated group developed decreases in *p*H, base excess, P_{O_2}, and oxygen saturation, and increases in P_{CO_2}. These signs of asphyxia were partially reversible. In contrast, there were no significant changes in fetal blood gases during infusion of ephedrine (table 5).

Discussion

The two pressors, methoxamine and ephedrine, were chosen for study not only because they are commonly used, but also because their modes of action differ. Methoxamine is the

TABLE 3. Uterine Blood Flow and O_2 Delivery during Infusion of Methoxamine and Ephedrine (Mean ± SD)

	Number of Subjects and Treatment	Control I	Test	Control II
Uterine blood flow (ml/min/kg)	6, methoxamine	98.0 ± 61.0	88.5 ± 52.0	134.2 ± 73.5
	6, ephedrine	61.2 ± 25.3	61.9 ± 26.6	54.7 ± 24.0*
Uterine blood flow (ml/min)	6, methoxamine	82.3 ± 53.2	68.7 ± 47.7	97.8 ± 61.8
	6, ephedrine	40.4 ± 12.8	40.1 ± 12.1	35.9 ± 12.3*
Uterine A-V_{O_2} difference (vol %)	8, methoxamine	4.4 ± 2.0	5.3 ± 2.1	4.5 ± 1.4
	6, ephedrine	6.9 ± 1.8	7.3 ± 1.8	6.5 ± 3.2
Uterine O_2 consumption (ml/min)	6, methoxamine	3.9 ± 1.3	4.0 ± 1.7	5.0 ± 2.8
	6, ephedrine	2.7 ± .9	2.5 ± .5	2.2 ± .6*

* Versus test, $P < 0.05$.

prototype of a pure alpha receptor stimulator or peripheral vasoconstrictor, while ephedrine possesses primarily beta receptor stimulating properties, with weak and unpredictable alpha stimulating properties.

The maternal hemodynamic data (fig. 1) emphasize the alteration in total peripheral resistance as the predominant change produced by methoxamine. This effect, the increase in arterial blood pressure, the decrease in heart rate, decline in cardiac output, and variable response in stroke volume, are similar to the findings of Li and associates in nonpregnant human beings.[14]

The chronotropic effects of ephedrine were frequently the only evidence of its activity. On occasion it was impossible to produce a 20 per cent increase in pulse rate. Contrary to expectations, cardiac output did not increase in response to ephedrine. It is possible that during the control periods these animals had high cardiac outputs which masked any subsequent effects of ephedrine.

The uterine blood flow and fetal blood gas data must be interpreted taking into account the limitations of the preparation. The experimental design was restricted to three periods because of the gradual deterioration of the preparation produced by the instrumentation and surgical manipulation.[15] A second control was necessary, therefore, to differentiate changes related to the test period from changes related to the underlying deterioration of the preparation.

The actual uterine blood flow values obtained by the steady-state diffusion technique were dependent upon the relative amounts of venous blood contained in the uterine venous samples, from the placenta, fetus and myometrium.[11] This ratio, while constant for one preparation, could be different for another because of a small variation in the location of the uterine venous catheter tip. In those instances where wide variation in absolute values was present, statistical analysis for significance was negative, but trends could be seen. The trend toward decreasing uterine blood flow during methoxamine and the lack of change during ephedrine infusion correlated well with the changes in maternal hemodynamics.

An additional, unexpected finding was the significant decline in uterine blood flow after ephedrine was stopped. Wislicki[16] reported 15 minutes of ganglionic blockade in cats following several intravenous injections of ephedrine, 10 mg/kg, over a 10-minute interval. He noted that various ganglia differ in their sensitivity to this blocking phenomenon. It is conceivable that the decrease in uterine blood flow after the termination of ephedrine was related to a ganglionic blockade in the uterus not present in some of the larger vascular beds. There are several ways in which our preparation differed from the usual clinical situation in which a prophylactic pressor is given intramuscularly, total dosages are smaller, and the interval of time between vasopressor administration and separation of the infant

TABLE 4. Fetal Cardiovascular Changes during Infusion of Methoxamine and Ephedrine (Mean ± SD)

	Number of Subjects and Treatment	Control I	Test	Control II
Heart rate (beats/min)	9, methoxamine	165 ± 14.0	136 ± 34.0†	155 ± 18.5
	6, ephedrine	167 ± 16.2	179 ± 31.4	162 ± 27.6*
Mean arterial blood pressure (mm Hg)	8, methoxamine	52.1 ± 11.2	54.4 ± 13.4	48.9 ± 19.3
	6, ephedrine	53.0 ± 6.4	50.8 ± 7.0	45.0 ± 10.4

* Versus test, $P < 0.05$.
† Versus control I, $P < 0.005$.

TABLE 5. Fetal Respiratory Gases during Infusion of Methoxamine and Ephedrine (Mean ± SD)

	Number of Subjects and Treatment	Control I	Test	Control II
pH	9, methoxamine	7.231 ± 0.153	7.044 ± 0.204§	7.128 ± 0.181
	6, ephedrine	7.232 ± 0.063	7.165 ± 0.173	7.126 ± 0.176*
P_{CO_2} (mm Hg)	9, methoxamine	55.1 ± 26	85.9 ± 43.3§	62.7 ± 21.2
	6, ephedrine	42.3 ± 4.2	49.5 ± 11.0	45.5 ± 15.9
P_{O_2} (mm Hg)	9, methoxamine	23.7 ± 6.9	17.5 ± 6.6†	22.7 ± 6.8
	6, ephedrine	19.2 ± 4.2	17.4 ± 3.3	14.8 ± 1.8
Base excess (mEq/l)	9, methoxamine	−6.7 ± 3.0	−11.6 ± 6.2‡	−11.8 ± 5.1
	6, ephidrine	−8.1 ± 4.3	−10.1 ± 5.3	−11.8 ± 4.5
O_2 saturation (per cent)	9, methoxamine	60.8 ± 18.9	30 ± 23.2§	42 ± 25.9
	5, ephedrine	38.5 ± 18.5	32.8 ± 15.2	26.8 ± 16.2

* Versus test, $P < 0.02$.
† Versus control I, $P < 0.025$.
‡ Versus control I, $P < 0.005$.
§ Versus control I, $P < 0.001$.

from its uterine environment is commonly shorter than the hour which elapsed before our decrease in uterine blood flow was observed. We were unable to record the times at which these changes began, and for this reason hesitate to endorse the prophylactic use of ephedrine during pregnancy. However, ephedrine remains the vasopressor of choice for the treatment of obvious spinal hypotension.

Fetal heart rate changes suggest the passage of pressors across the placenta. Although phenylephrine, levarterenol, and angiotension do not cross the ovine placenta,[17] transmission of isotope-labelled norepinephrine across the human placenta has been reported.[18] The transplacental passage of vasopressors has not been definitively studied. The effects of concentration and the possibility that vasopressors move transplacentally in altered form have not been evaluated. The decrease in fetal heart rate with methoxamine and the increase in fetal heart rate with ephedrine could also represent responses to severe and mild hypoxia, respectively. The fetal P_{O_2} and O_2 saturations were comparable during the test periods, but a greater relative change was present in the methoxamine group. It is difficult to separate cause and effect. There is a need to study the effects of alterations in fetal or placental circulation on the overall fetal–maternal exchange. If the fetal response to

methoxamine consisted of bradycardia, decrease in cardiac output, and increase in total peripheral resistance, as in the mother, this could cause fetal harm in addition to that produced by a decline in uterine blood flow alone. Similarly, perhaps part of the benign fetal course with ephedrine is due to its beneficial effect or the lack of any effects on the fetal circulation.

It is apparent that methoxamine can cause fetal asphyxia if given to pregnant monkeys which are normotensive. Our data support a fall in uterine blood flow as the cause. In addition, there may be constriction of the spiral arterioles or the umbilical vessels or an increase in placental shunting. Ephedrine is a relatively innocuous drug to give in the presence of normotension, but during recovery from its administration there are changes in uterine blood flow which are potentially as harmful as those seen with methoxamine.

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