

# An Evaluation of Vasopressor Therapy for Maternal Hypotension during Spinal Anesthesia

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During hypotension resulting from conduction anesthesia in gravid ewes, uterine blood flow (UBF) decreased roughly in proportion to the decrease in maternal blood pressure. Ephedrine or mephentermine significantly increased UBF over that accomplished by metaraminol. Presumably, the preferential effects of these agents were the result of increased cardiac output owing to inotropic and chronotropic actions. However, UBF never exceeded 90 per cent of prespinal levels with any vasoactive agent and, for a given maternal system, the UBF response was variable, generally increasing but frequently remaining constant or decreasing. For these reasons, all other methods of combating hypotension should be used initially. If vasopressors are still required, agents of choice are those whose principal mode of action lies in cardiac stimulation rather than peripheral vasoconstriction. (Key words: Vasopressors; Spinal anesthesia; Hypotension; Pregnancy.)

In 1965, Greiss and Crandell<sup>1</sup> found that in pregnant sheep maternal hypotension from spinal anesthesia was associated with a proportionate decrease in uterine blood flow (UBF). They showed that norepinephrine (Levophed), phenylephrine (Neosynephrine) and angiotension amide (Hypertensin-CIBA) therapy caused sufficient uterine vasoconstriction to negate the effects of increased blood pressure so that UBF was not increased. From these data, they generalized that under these circumstances vasopressor agents should be used only as a last resort for maternal well-

being and that the fetal environment should not be expected to improve. These conclusions have been questioned, since consideration was not given to the duality of action (peripheral vs. central effects) of vasopressor agents. In a similar series of experiments, Lucas and associates<sup>2</sup> showed that slow infusions of metaraminol (Aramine) simultaneously restored maternal blood pressure (MBP) and UBF to normal levels after 30 minutes. However, UBF remained low during the first ten minutes of therapy, and the prolonged duration of treatment was not only impractical clinically but precluded an evaluation of the contribution of the normal compensatory responses to spinal hypotension. Recently, Shnider and associates<sup>3</sup> induced similar hypotension in gravid ewes and reported that fetal bradycardia was corrected and fetal acidosis was decreased after restoration of MBP with ephedrine. However, UBF was not monitored in these experiments, the time relationships did not simulate clinical conditions, and significant fetal metabolic acidosis persisted in three of eight trials.

On this background, the present experiments were performed to assess more thoroughly the efficacy of metaraminol and ephedrine, as well as the primarily centrally-acting mephentermine (Wyamine) on the correction of spinal hypotension during pregnancy.

## Methods

Fasted Western ewes between 70 and 140 days of gestation and weighing 41 to 54 kg were studied. Each ewe was placed in the right lateral decubitus position and a polyvinyl catheter inserted percutaneously into the external jugular vein. The ewes were ventilated with a Harvard small-animal respirator after an airway had been established by tracheal intubation aided by paralysis with *d*-tubocurarine chloride, 9.0 mg, or tracheostomy

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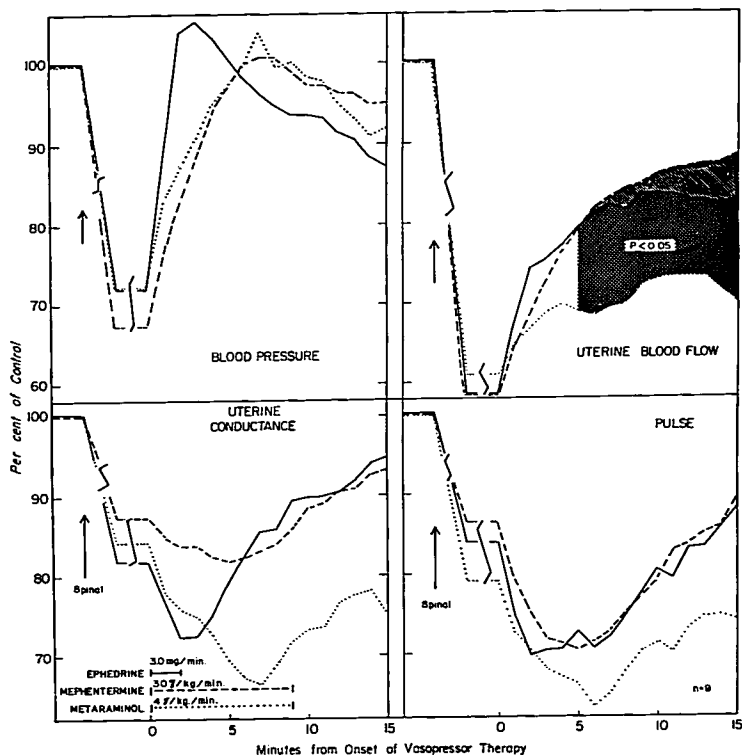
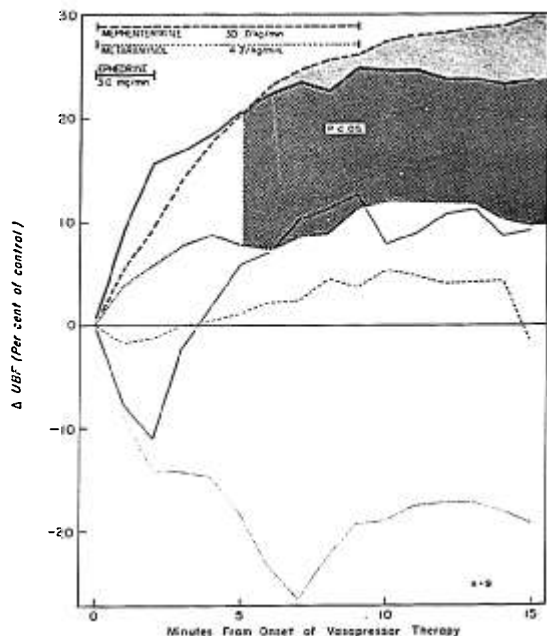


FIG. 1. Average response patterns to ephedrine and slow infusions of mephentermine and metaraminol following hypotension induced by spinal anesthesia. After four minutes, uterine blood flow was significantly higher with ephedrine or mephentermine than with metaraminol therapy. In this and subsequent figures,  $P$  values were calculated from the differences between spinal hypotensive rates and therapy rates ( $\Delta$ UBF).

under 1.0 per cent lidocaine (Xylocaine) anesthesia. A Foregger anesthesia machine delivered appropriate concentrations of nitrous oxide and oxygen to the intake cylinder of the respirator. We adjusted tidal volume, respiratory rate and gas concentrations to maintain normal arterial blood pH,  $P_{CO_2}$  and  $P_{O_2}$  levels. In all experiments, the nitrous oxide-oxygen ratio varied between 4:1 to 3:1 during the operative procedures. Thereafter, 2:1 or 1:1 ratios were often required to maintain

normal  $Pa_{O_2}$  levels. Zero occlusion loops and electroamagnetic flow probes were implanted around the descending aorta and the left middle uterine artery, respectively, as previously described.<sup>4,5</sup> A polyvinyl catheter was passed via a gluteal branch of the femoral artery into the descending aorta and connected to a Statham P23AA pressure transducer for arterial blood pressure monitoring, and a similar catheter was inserted into a leg vein for infusion of drugs. After the completion of all procedures,

FIG. 2. Comparison of variations of UBF responses shown in figure 1. Light lines describe curves of  $-2$  standard deviations around the mean response (heavy lines). With ephedrine and mephentermine, UBF rarely decreased below spinal hypotensive levels. With metaraminol, UBF frequently decreased further during therapy.



we connected the pressure transducer and the flowmeter to separate channels of a Dynograph. A cardi tachometer triggered from the preamplifier output of the MBP channel monitored maternal heart rate (MHR). Maternal arterial blood samples were obtained anaerobically from the MBP catheter and analyzed immediately with appropriate electrodes for pH,  $P_{CO_2}$  and  $P_{O_2}$ .

Following operation, the condition of the ewes stabilized for 30 to 60 minutes. Nitrous oxide and oxygen flows and ventilation were adjusted during this time to achieve acceptable blood gas tensions (pH 7.35-7.50;  $P_{aCO_2}$  25-35 mm Hg;  $P_{aO_2}$  80-150 mm Hg). After lumbar puncture at the  $L_2L_3$ - $L_3L_4$  level, the administration of equal parts of 1 per cent tetracaine (Pontocaine) and 10 per cent dextrose in water produced high spinal anesthesia. Usually, 40 to 80 mg of tetracaine were re-

quired to achieve significant maternal hypotension. After stabilization of all parameters at hypotensive levels (10 to 15 min), a Harvard infusion pump delivered test drugs intravenously as follows:

A) metaraminol, 4  $\mu$ g/kg/min and mephentermine 30  $\mu$ g/kg/min for nine minutes ephedrine sulfate, 3.0 mg/min (70  $\mu$ g/kg/min) for two minutes. (Vasopressors were discontinued when maternal blood pressure surpassed prespinal control levels.)

B) metaraminol, mephentermine and ephedrine at rates necessary to restore normotension as rapidly as possible.

C) B plus atropine sulfate, 0.8 mg intravenously, within 30 seconds of initiation of each therapy.

After vasopressor infusion, we observed maternal changes until return to approximate ( $\pm 10$

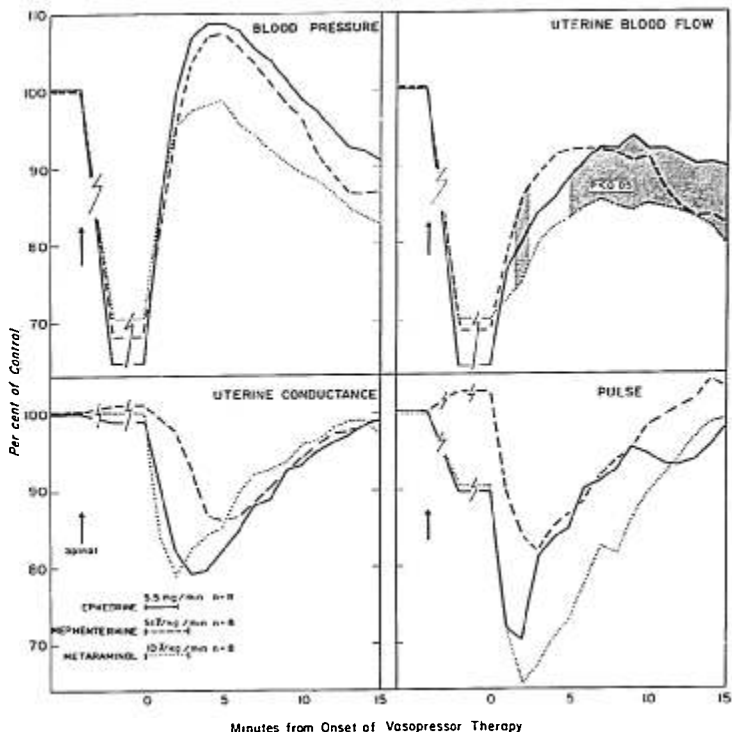


FIG. 3. Average response patterns to rapid infusions of ephedrine, mephentermine and metaraminol. Although the responses were similar to those following slower infusions, fewer significant differences in  $\Delta$ UBF indicate a greater degree of uterine vasoconstriction.

per cent) pretherapy levels; frequently, this required supplemental doses of intrathecal tetracaine to maintain spinal anesthesia and to reproduce maternal hypotension. The sequence of test treatments was randomized in each experiment to offset the effects of time and previous treatment on the experimental preparation. At the completion of each experiment, cesarean section revealed live fetuses in all but one case.

For comparison between experiments, we expressed changes in all variables as per cent of the average of seven observations taken at

five-minute intervals during a 30-minute control period. UBF, uterine vascular conductance (UVC), MBP and MHR were calculated during the stable hypotensive period and at one-minute intervals for 15 minutes during, and following, therapies. UVC was determined from the equation,  $UVC = UBF/MBP$ . A value for UVC of less than 100 per cent of control is indicative of vasoconstriction and a value greater than 100 per cent, of vasodilatation. Data were analyzed for significance with Student's *t* test. Values of  $P < 0.05$  were considered to be significant.

**Results**

We tested 80 treatments in 14 ewes. Initial spinal anesthesia sufficient to cause a 29 per cent fall in mean MBP and a 14 per cent fall in MHR resulted in a 42 per cent decrease in UBF. UVC decreased 18 per cent, but with time and additional intrathecal medication UVC gradually increased to control values.

The effects of slow infusions of metaraminol, mephentermine, and ephedrine (protocol A) were compared in nine ewes (fig. 1). MBP increased to 90 per cent of control within three minutes and obtained control levels by six minutes with metaraminol and mephentermine, while the dose of ephedrine caused such

a rapid rise in MBP that the infusion was discontinued after two minutes. The pattern of initial decrease and later increase in UVC and MHR was observed with all agents, but the changes were more marked with metaraminol. UBF increased with all drugs tested, but from four to 15 minutes after initiation of therapy, mephentermine and ephedrine caused significantly greater changes ( $P < 0.05$ ) from hypotensive levels ( $\Delta$ UBF) than metaraminol (fig. 2). At best, UBF never exceeded 90 per cent of prespinal flow rates. For a given ewe, the changes in UBF were variable with all agents. While mephentermine and ephedrine usually increased UBF at least minimally,

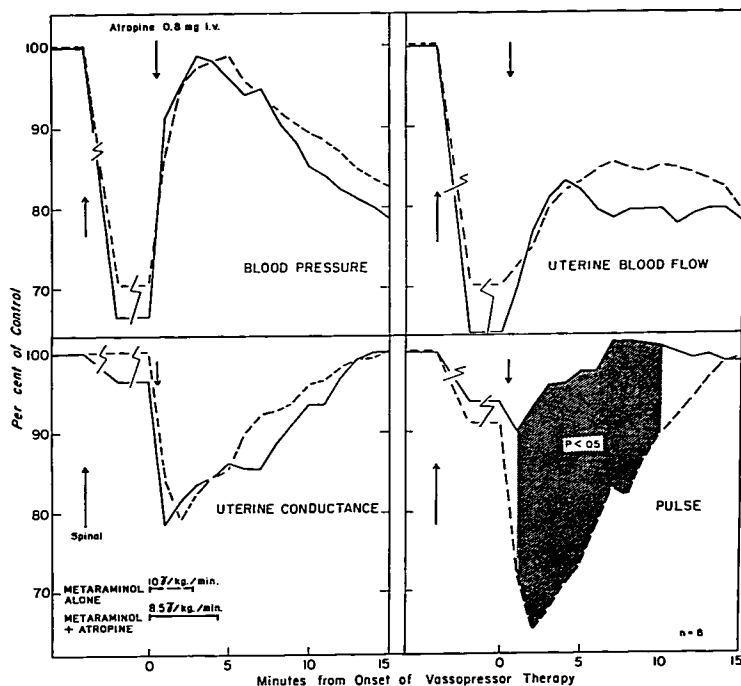


FIG. 4. Comparison of response patterns using metaraminol with and without atropine. Although atropine blocked reflex bradycardia, similar doses of metaraminol were required to achieve normotension and UBF changes were similar.

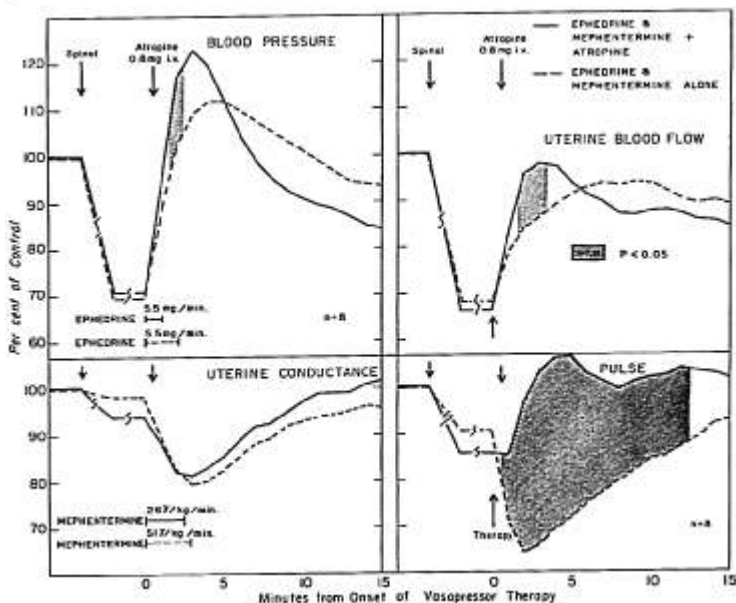


FIG. 5. Comparison of response patterns using ephedrine and mephentermine with and without atropine. Atropine halved the doses required to achieve normotension and reversed bradycardia to tachycardia so that significant improvement in UBF resulted.

metaraminol frequently decreased UBF to below pretreatment levels (see curves of  $-2$  SD, fig. 2).

In eight ewes, rapid infusions of metaraminol ( $10 \mu\text{g}/\text{kg}/\text{min}$ ), mephentermine ( $51 \mu\text{g}/\text{kg}/\text{min}$ ) and ephedrine ( $5.5 \text{ mg}/\text{min}$ ) achieved control MBP levels within two minutes. Infusions were discontinued after 2.75, 2.8 and 2.1 minutes, respectively. In general, the patterns of response resembled those after slower infusions, but the increase in UBF with mephentermine occurred more rapidly (fig. 3). The ephedrine:metaraminol  $\Delta\text{UBF}$  difference was significant ( $P < 0.05$ ) after four minutes of therapy, while the mephentermine:metaraminol difference was significant only at two minutes, remaining between  $P < 0.10$  and  $P > 0.05$  through ten minutes.

With comparable infusions of metaraminol ( $8.5 \mu\text{g}/\text{kg}/\text{min} \times 4.3 \text{ min}$  vs.  $10 \mu\text{g}/\text{kg}/\text{min} \times 2.75 \text{ min}$ ) in eight ewes, atropine eliminated bradycardia but caused essentially no changes in the other variables (fig. 4). In contrast, atropine halved the required doses of mephentermine and ephedrine, blocked bradycardia, and accomplished a significant  $\Delta\text{UBF}$  difference from two to four minutes after onset of therapy (fig. 5). (The responses with mephentermine and ephedrine were so similar when compared with Student's  $t$  test that they were pooled for statistical purposes.)

Graphs of the pooled effects of each vasopressor agent tested under all of the various experimental conditions appear in figures 6 and 7. Consistently, mephentermine and ephedrine caused less uterine vasoconstriction

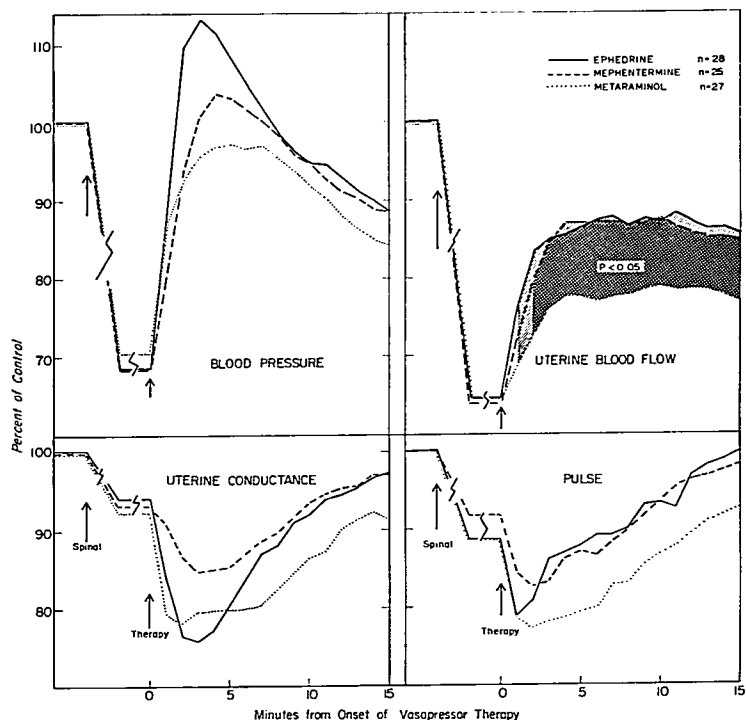


FIG. 6. Pooled average response patterns to ephedrine, mephentermine and metamamol given at varying rates with and without atropine. After one and two minutes with ephedrine and mephentermine, respectively,  $\Delta$ UBF was significantly higher than with metamamol.

per unit MBP rise, less bradycardia, and a greater increase in UBF than metamamol. The ephedrine:metamamol  $\Delta$ UBF difference was significant ( $P < 0.01$ ) at all times after initiation of therapy, and the mephentermine:metamamol difference was significant ( $P < 0.05$  to  $< 0.01$ ) between two and 15 minutes. Mephentermine and ephedrine increased UBF roughly 10 per cent of prespinal levels more than metamamol, but at best UBF was still 15 per cent below prespinal rates. In addition, the curves of  $-2$  SD in

the pooled rate (fig. 7) demonstrate the wide variability of individual responses.

### Discussion

Spinal anesthesia induces systemic hypotension by two principal mechanisms, interruption of preganglionic sympathetic nerve impulses and decreased cardiac output secondary to peripheral pooling of blood and decreased venous return to the heart. The latter is associated with bradycardia. According to Greene,<sup>6</sup> systolic hypotension to 90 mm Hg is

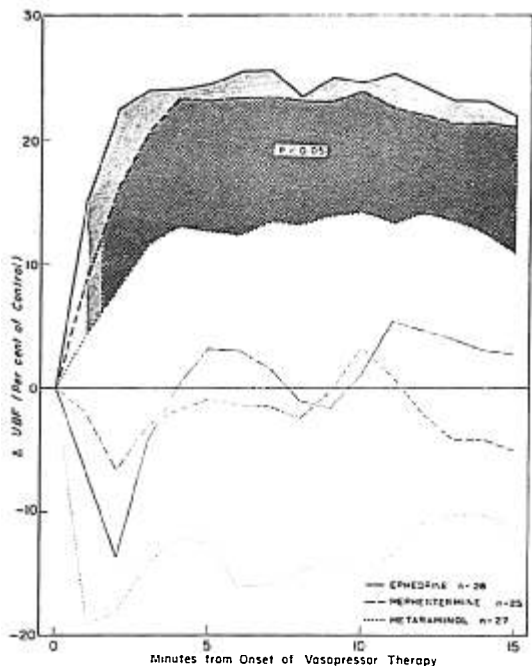


FIG. 7. Comparison of variations in UBF responses shown in figure 6. The upper three heavy lines represent mean values of UBF; the lower three light lines are the curves of  $-2$  standard deviations of UBF. With ephedrine and mephentermine, the curves of  $-2$  SD (light lines) fluctuated around the pretherapy UBF rates. With metaraminol the curve of  $-1$  SD (if plotted) would fluctuate about pretherapy UBF rates, indicating a 15 per cent chance of further decreasing UBF.

caused by decreased arteriolar resistance while more profound hypotension develops from decreased cardiac output. In pregnancy, pressure on the vena cava from the gravid uterus enhances peripheral pooling of blood and increases the degree of hypotension. In the present study, the lateral decubitus position and anatomic differences in the ovine uterus and extremities necessitated the induction of high spinal anesthesia before marked hypotension occurred. Bradycardia could not be considered an index of decreased cardiac output since sympathetic cardiac accelerator fibers probably were paralyzed. Therefore, when extrapolating the present results to the clinical situation, one must remember that decreased arteriolar resistance probably played a greater role in inducing hypotension than is usual in

pregnant women. If hypotension could be avoided a major disadvantage of spinal anesthesia for cesarean sections would be eliminated. Many prophylactic measures can be used to prevent hypotension in the pregnant woman. These include lower doses of intrathecal agents, preloading of the circulatory blood volume with rapidly infused intravenous fluids,<sup>7</sup> placing the patient in a mild degree of Trendelenburg position, and left uterine displacement. Preliminary results with inflatable boots demonstrate that by decreasing peripheral pooling of blood in the legs the problem of hypotension is diminished.<sup>8</sup> However, despite all of these measures significant hypotension still occurs. Under these circumstances, vasopressor therapy should also be directed toward augmenting cardiac output



rather than increasing arteriolar resistance. This is particularly true in pregnancy where, under resting conditions, the uterine vascular bed is almost maximally dilated.<sup>9</sup> Further uterine vasodilatation does not occur as a result of sympathetic nerve block so that vasoconstrictor agents, simultaneously affecting the uterine and peripheral beds, negate or diminish the beneficial effects of increased blood pressure. To combat maternal hypotension during spinal anesthesia a vasopressor agent should stimulate cardiac rate and contractility and constrict capacitance vessels while not affecting resistance vessels.

Mephentermine has a minimal effect upon peripheral arteriolar resistance, acting primarily via cardiac stimulation and vasoconstriction.<sup>10-15</sup> Ephedrine stimulates both alpha and beta receptors. However, cardiac stimulation is a more prominent action, so that the negative effect of peripheral vasoconstriction on UBF is partially overcome.<sup>10-12</sup> Metaraminol also stimulates both alpha and beta receptors; but the alpha effect is dominant, so that the drug, particularly in high concentrations, acts primarily by increasing peripheral resistance.<sup>10, 14, 15, 16</sup> Drug concentration is also important with mephentermine and ephedrine, higher doses causing greater alpha-receptor stimulation. In addition, the effects of these agents depend upon the cardiovascular status before administration. For example, during spinal hypotension mephentermine acts primarily on the heart if initial cardiac output is low, but if the initial cardiac output is high, the drug acts by increasing peripheral resistance.<sup>17</sup>

The present results corroborate responses predictable from the reported characteristics of the three agents tested. Because of its predominant effects, mephentermine was the theoretical agent of choice; however, both it and ephedrine improved UBF similarly. UVC was decreased least by mephentermine and excessive increases in maternal blood pressure were avoided more easily with this agent. Blockade of the baroreceptor reflex with atropine facilitated the positive inotropic and chronotropic actions of mephentermine and ephedrine, permitting a significantly greater increase in UBF with only half the dose required with-

out atropine. With metaraminol, atropine blocked reflex bradycardia, but UBF responses were similar at dose levels equivalent to those when atropine was not employed.

Mephentermine and ephedrine were superior to metaraminol in improving UBF. The variability of responses clearly demonstrates this superiority. Figure 2 depicts response variability with one mode of treatment and figure 7 illustrates variability with the pooling of multiple therapeutic regimes. The latter were described since variable rates of administration with and without atropine more closely approximate the variety of ways the clinician employs vasopressors. At the least, mephentermine and ephedrine left UBF unchanged while restoring normotension. With metaraminol, there was a 15 per cent chance of a further reduction in UBF. Most significant of all these observations is that some uterine vasoconstriction was evoked by all agents tested with all modes of therapy, so that at best, UBF was never increased above 85 to 90 per cent of prespinal rates. Therefore, while vasopressor therapy with ephedrine or mephentermine or similar agents has an undisputable place in the therapy of spinal hypotension in pregnancy, it can never be considered optimal and should be reserved for circumstances in which all other measures have failed.

## References

1. Greiss, F. C., Jr., and Crandell, D. L.: Therapy for hypotension induced by spinal anesthesia during pregnancy, *J.A.M.A.* 191: 793, 1965.
2. Lucas, W., Kirschbaum, T., and Assali, N. S.: Spinal shock and fetal oxygenation, *Amer. J. Obstet. Gynec.* 93: 583, 1965.
3. Shnyder, S. M., de Lorimier, A. A., Holl, J. W., Chapler, F. K., and Morishima, H. O.: Vasopressors in obstetrics. I. Correction of fetal acidosis with ephedrine during spinal hypotension, *Amer. J. Obstet. Gynec.*, 102: 911, 1968.
4. Greiss, F. C.: A mechanical zero reference for implanted flowmeter systems, *J. Appl. Physiol.* 17: 177, 1962.
5. Greiss, F. C.: The uterine vascular bed: Effect of adrenergic drug stimulation, *Obstet. Gynec.* 21: 295, 1963.
6. Greene, W. M.: *Physiology of Spinal Anesthesia*, Baltimore, Williams & Wilkins Co., 1969.

7. Wollman, S. B., and Marx, G. F.: Acute hydration for prevention of hypotension of spinal anesthesia in parturients, *ANESTHESIOLOGY* 29: 374, 1968.
8. Barclay, D. L., and Renegar, O. J.: Unpublished observations.
9. Greiss, F. C., Jr.: Pressure-flow relationship in the gravid uterine vascular bed, *Amer. J. Obstet. Gynec.* 96: 41, 1966.
10. Aviado, D. M., Jr.: Cardiovascular effects of some commonly used pressor amines, *ANESTHESIOLOGY* 20: 71, 1959.
11. Goldberg, L. I., Cotton, M. deV., Darby, T. D., and Howell, E. V.: Comparative heart contractile force effects of equipressor doses of several sympathomimetic amines, *J. Pharmacol. Exp. Ther.* 108: 177, 1953.
12. Innes, I. R., and Nickerson, M.: In Goodman, L. S., and Gilman, A. (eds.): *The Pharmacological Basis of Therapeutics*. New York, MacMillan, 1965, pp. 503-508.
13. Li, T. H., Shimosata, S., and Etsten, B.: Hemodynamics of mephentermine in man, *New Eng. J. Med.* 267: 180, 1962.
14. Lewis, C. M., and Weil, W. H.: Hemodynamic spectrum of vasopressor and vasodilator drugs, *J.A.M.A.* 208: 1391, 1969.
15. Weil, M. H., and Bradley, E. C.: Circulatory effects of vasoactive drugs in current use for treatment of shock: A reclassification based on experimental and clinical study of their selective arterial and venous effects, *Bull. N. Y. Acad. Med.* 42: 1023, 1966.
16. Sarnoff, S. J., Case, R. B., Berglund, E., and Sarnoff, L. C.: Ventricular function: V. The circulatory effects of aramine: Mechanism of action of vasopressor drugs in cardiogenic shock, *Circulation* 10: 84, 1954.
17. Ritchie, J. M., Cohen, P. J., and Drripps, R. D.: In Goodman, L. S., and Gilman, A. (eds.): *The Pharmacological Basis of Therapeutics*. New York, MacMillan, 1965, p. 390.

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### Drugs

**ARTERIAL INJURIES** Thirty-one patients with arterial injuries were treated over a five-year period in one hospital. Of these, 15 had injuries which had occurred in connection with arterial catheterization. Ten had thrombosis which required operation. Presumably this resulted from single small intimal lesions plus compression. In one case the intima was loosened, forming a valve mechanism. In two cases calcified plaques were loosened. Two patients had hematomas which required drainage. The vessels included femoral, popliteal, subclavian, axillary and brachial arteries. A misdiagnosis of spasm delays treatment and may necessitate amputation. If circulation is not restored within a few hours after treatment with sympatholytic drugs or sympathetic block, the artery should be explored. (*Eriksen, H. C., and Sprensen, H. H.: Arterial Injuries, Iatrogenic and Non-iatrogenic, Acta Chir. Scand.* 135: 133 (No. 2) 1969.)

**INTRAVASCULAR CATHETERS** Clotting was measured on the external surfaces of catheters made of various materials after they had been left in the carotid arteries or jugular veins of dogs. Without heparin protection, surface clotting in significant amounts was found on all catheters, and emboli could easily have been stripped from the surface on withdrawal of the catheter. A small degree of systemic heparinization practically eliminated surface clotting on all catheters. Mild systemic heparinization with a single slow injection soon after such a catheter is inserted in a vessel, with neutralization of the heparin effect by injection of protamine about two minutes before withdrawal of the catheter, is recommended. (*Nejad, M. S., and others: Clotting on the Outer Surfaces of Vascular Catheters, Selected Papers of Carle Clinic and Carle Foundation* 22: 8 (July) 1969.)