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Effects of Nitroglycerin and Nitroprusside on the Uterine Vasculature of Gravid Ewes

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The effects of nitroglycerin (TNG) and sodium nitroprusside (SNP) on mean aortic pressure (MAP), uterine blood flow (UBF), uterine vascular conductance (UVC), and pulse rate (PR) were compared when the two agents were infused to prevent and treat hypertension induced by norepinephrine (NE) in gravid ewes. When infused alone, TNG, 19 μg/kg/min, decreased MAP 19 per cent and increased PR 33 per cent from control values ($P < 0.05$), but did not significantly change UBF or UVC. In comparison, SNP, 3 μg/kg/min, decreased MAP 20 per cent and increased PR 43 per cent ($P < 0.05$), and did not significantly change UBF or UVC. When given alone, four successive 2-min infusions of NE produced dose-related increase in MAP and decreases in UBF, UVC, and PR; values were significantly different from control with the two higher doses of NE. Although MAP, UBF, and UVC were still significantly changed from control levels when NE was given in the presence of the above infusions of TNG or SNP, MAP was lower and UBF and UVC were higher compared with when NE was given alone ($P < 0.05$). When given to control hypertension induced by a continuous infusion of NE, TNG or SNP produced uterine vasodilatation and significantly increased UBF. Nitroglycerin and SNP were equally effective in counteracting the maternal hypertension and antagonizing the uterine vascular effect of NE. It is concluded that TNG and SNP counteract uterine vasoconstriction resulting from alpha-adrenergic stimulation and do not produce a shunt of blood flow away from the uterine vasculature when used to control hypertension in gravid ewes. (Key words: Anesthesia, obstetric. Blood pressure: hypertension. Uterus: blood flow.)

IN PATIENTS with severe hypertension of pregnancy, alarming increases in blood pressure often accompany laryngoscopy and tracheal intubation during general anesthesia for cesarean section. Intracranial hemorrhage and cardiac failure are possible sequelae. The safety of general anesthesia can be increased by controlling hypertension with intravenous administration of an antihypertensive agent. However, none of the commonly used agents, such as hydralazine, phentolamine, sodium nitroprusside, or trimethaphan, is ideal when considering the effects of each drug on mother and fetus. Nitroglycerin, an effective antihypertensive drug,[1,2] may be suitable for use during cesarean section, but its effects on the uterine vasculature are unknown. We compared the effects of nitroglycerin (TNG) and nitroprusside (SNP) on uterine blood flow and uterine vascular conductance before and during infusions of norepinephrine (NE) in gravid ewes.

Methods

Fasted ewes, 100 to 130 days' gestation (term 145 days), were sedated with pentobarbital, 6 mg/kg, intravenously, and placed in the right lateral decubitus position. Anesthesia was induced and maintained with ketamine (induction dose, 4 mg/kg; maintenance dose, 3 mg/kg/hr, intravenously). Through a left inguinal incision, a mammary artery was cannulated for measurement of mean aortic pressure (MAP) and a mammary vein was cannulated for infusions of norepinephrine. Square-wave electromagnetic flow transducers†† and zero-occlusion loops[3] were implanted around the left uterine artery and the descending aorta, respectively, for measurement of uterine blood flow (UBF). A pressure balloon was placed between the chorion and uterine wall for direct intrauterine pressure (IUP) measurements.

Following a minimum three-day postsurgical period, the UBF tracings were observed daily to determine whether the effects of surgical manipulation and instrumentation had dissipated. On the day of investigation, the pressure and flow transducers were connected to separate channels of a dynograph‡‡ while the ewes were standing in a dark, quiet room. Continuous recordings of MAP, UBF, IUP, and pulse rate

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TABLE 1. Aortic Pressure, Uterine Blood Flow, Uterine Vascular Conductance, and Pulse Rate Values (Mean ± SEM) before and during Infusions of Nitroglycerin, 19 μg/kg/min, and Nitroprusside, 3 μg/kg/min, with Percentage Changes from Control

	Nitroglycerin (TNG) (n = 7)			Nitroprusside (SNP) (n = 7)		
	Control	During TNG	Change (Per Cent)	Control	During SNP	Change (Per Cent)
Mean arterial pressure (torr)	83 ± 3	66 ± 2*	−19 ± 1	81 ± 2	65 ± 2*	−20 ± 2
Uterine blood flow (ml/min)	381 ± 24	356 ± 23	−7 ± 2	370 ± 20	333 ± 22	−10 ± 3
Uterine vascular conductance (ml/min/torr)	4.7 ± 0.4	5.4 ± 0.4	+16 ± 3	4.6 ± 0.3	5.1 ± 0.4	+13 ± 3
Pulse rate (beats/min)	102 ± 7	136 ± 12*	+33 ± 7	104 ± 4	145 ± 13*	+43 ± 9

* $P < 0.05$, values of variables versus control levels.

(PR) were observed until stable, following which vasoactive drugs were given intravenously by an infusion pump.§§ In Phase I of the study, 11 infusions of norepinephrine (NE) were given alone and in the presence of TNG and SNP in seven ewes to determine the efficacy of either agent for preventing the vascular responses to NE. Norepinephrine was infused alone for 2-min periods at successive rates of 0.1, 0.2, 0.5, and 1.0 μg/kg/min; vascular variables returned to control levels between doses. Nitroglycerin, 500 μg/ml, and SNP, 250 μg/ml, were infused alone to decrease MAP by 15 to 25 per cent for a period of 10 min. While continuing the infusion of the antihypertensive agents, the four infusions of NE were successively given as described above. During the course of the study, the sequence of drug administrations (NE alone, TNG plus NE, and SNP plus NE) was randomized to decrease experimental bias. Vascular variables returned to control levels before each sequence.

In Phase II of the study, NE, 13 μg/ml, was infused in ten experiments in eight ewes to increase MAP by 20 to 25 per cent for a period of 10 min. While continuing the infusion of NE, TNG or SNP was infused to return MAP to control levels for 10 min. Both drugs were discontinued, and when vascular variables had returned to control levels, the sequence was repeated with the other antihypertensive agent.

Mean aortic pressure and UBF values were sampled every 10 sec for a 30-sec period immediately before and during the maximal effect of each drug infusion. Uterine vascular conductance (UVC), the reciprocal of resistance, was estimated at each 10-sec interval (UVC ~ UBF/MAP) and averaged to determine control and response conductances. Changes in UVC, as well as maximal changes in MAP, UBF, and PR, were expressed as mean percentage change (± standard error of the mean) from control values immediately preceding each sequence. Data were analyzed with analysis of variance and the Student t test for paired samples; significance was assumed with $P < 0.05$.

§§ Harvard Apparatus Company, Dover, Mass.

Results

When infused alone to decrease MAP by 15 to 25 per cent, TNG (mean dose 19 μg/kg/min) and SNP (3 μg/kg/min) produced significant decreases in MAP and increases in PR, while UBF and UVC were not significantly changed from control values (table 1). Although statistically insignificant, the increases in UVC seen with both agents accounted for smaller respective changes in UBF than would be predicted from changes in MAP. Intrauterine pressure was not changed by TNG or SNP.

Before infusion of the four successive doses of NE, control values were MAP 83 ± 2 torr, UBF 362 ± 19 ml/min, UVC 4.5 ± 0.3 ml/min/torr, and PR 104 ± 6 beats/min. Norepinephrine alone produced a dose-related increase in MAP and dose-related decreases in UBF, UVC, and PR (figs. 1 and 2); the changes were significant with the 0.5 and 1.0 μg/kg/min doses of NE. Mean aortic pressue, UBF, and UVC were also changed significantly from control levels when NE was given in the presence of TNG, 19 μg/kg/min, or SNP, 3 μg/kg/min (figs. 1 and 2). However, MAP was significantly lower and UBF and UVC values were significantly higher when NE was given with both antihypertensive agents, in comparison with when it was infused alone. While equally preventing the hypertension, TNG and SNP similarly counteracted the effect of NE on the uterine vasculature (figs. 1 and 2).

In Phase II of the study, a continuous infusion of NE, mean dose 0.5 μg/kg/min, significantly increased MAP by 22 per cent, decreased UBF 39 per cent, and decreased UVC 49 per cent from control values (table 2). The addition of TNG, 25 μg/kg/min, returned MAP to 4 per cent below control values while increasing UVC and UBF. Although UBF and UVC did not return to control levels, they increased by 23 and 52 per cent, respectively, above values observed with NE alone, $P < 0.05$. Similar results occurred during infusions of SNP, 4 μg/kg/min, which decreased MAP to 4 per cent below control levels (table 2) and increased UBF and UVC by 26 and 51 per cent, re-

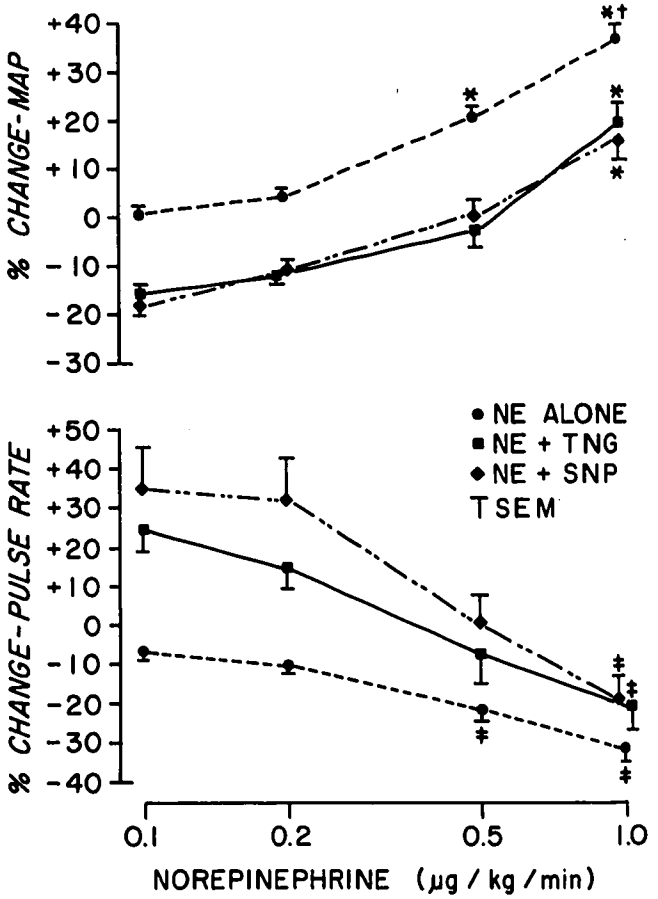

FIG. 1. Mean percentage changes of mean aortic pressure (MAP) and pulse rate from control when norepinephrine (NE) was infused for 2-min periods at rates of 0.1, 0.2, 0.5, and 1.0 μg/kg/min either alone or in the presence of nitroglycerin (TNG), 19 μg/kg/min, or sodium nitroprusside (SNP), 3 μg/kg/min. * $P < 0.05$, MAP higher than control. † $P < 0.05$, MAP with NE alone versus MAP with NE in the presence of TNG or SNP. ‡ $P < 0.05$, pulse rate lower than control. n = 7.

spectively, above levels observed during infusions of NE ($P < 0.05$). There were several experiments in which infusions of TNG and SNP did not increase UBF. However, neither agent was associated with a decrease in UBF when infused to return MAP to control levels.

Discussion

In patients with severe hypertension of pregnancy, we frequently administer antihypertensive agents intravenously to decrease blood pressure by 20 to 25 per cent before induction of general anesthesia for cesarean section. The agents are continued as needed to dampen the response to laryngoscopy and tracheal intubation. Since preeclamptic patients have increased sensitivity not only to alpha-agonistic compounds but also to other vasopressor substances, *e.g.*, angiotensin,[4] the alpha-blocking agents such as phentolamine are at best moderately effective for controlling hypertension. The nonspecific vascular smooth muscle relaxants having a rapid onset of action and a short duration of effect are most suitable for this purpose.

Although this practice may increase maternal safety of general anesthesia, these drugs may cause proportionately greater vasodilatation in the nonuterine vasculature, thereby producing a shunt or steal of blood flow away from the uterine vasculature. Ring *et al.*[5] studied changes in UBF and other maternal and fetal variables when hydralazine and SNP were given to counteract hypertension induced by phenylephrine in gravid ewes. While returning MAP to control levels, hydralazine therapy was associated with an increase

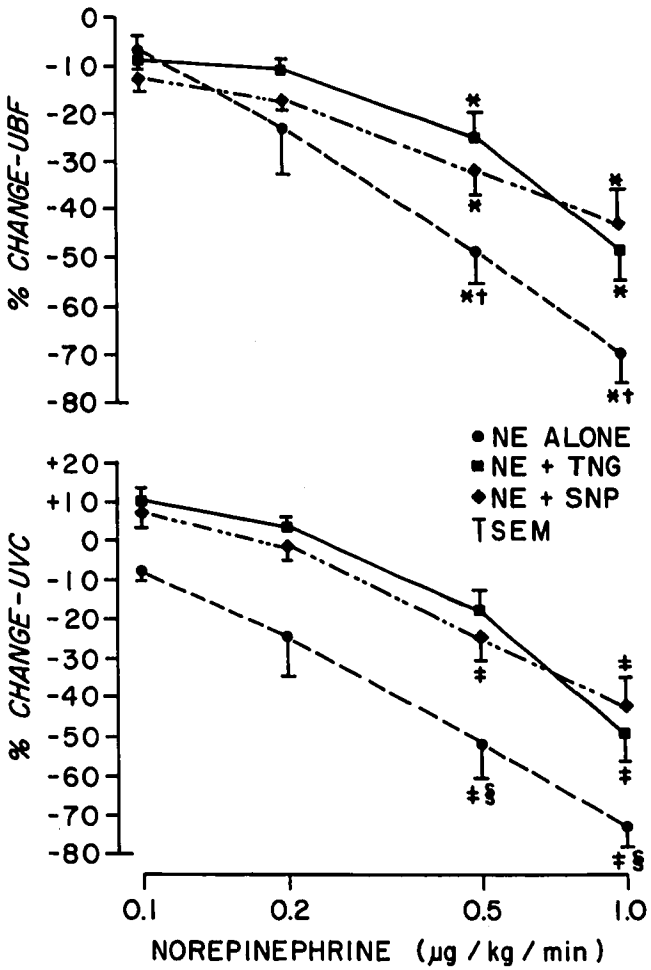

FIG. 2. Mean percentage changes of uterine blood flow (UBF) and uterine vascular conductance (UVC) from control when norepinephrine (NE) was infused for 2-min periods at rates of 0.1, 0.2, 0.5, and 1.0 μg/kg/min either alone or in the presence of nitroglycerin (TNG), 19 μg/kg/min, or sodium nitroprusside (SNP), 3 μg/kg/min. * $P < 0.05$, UBF versus control. † $P < 0.05$, UBF with NE alone versus UBF with NE in presence of TNG or SNP. ‡ $P < 0.05$, UVC versus control. § $P < 0.05$ UVC with NE alone versus UVC in the presence of TNG or SNP. n = 7.

TABLE 2. Changes (Mean ± SEM) of Mean Aortic Pressure, Uterine Blood Flow, Uterine Vasculature Conductance, and Pulse Rate from Control Values during Continuous Infusions of Norepinephrine (NE), 0.5 μg/kg/min, and during Control of Hypertension with Nitroglycerin, 25 μg/kg/min, and Nitroprusside, 4 μg/kg/min

	Nitroglycerin (TNG) (n = 8)			Nitroprusside (SNP) (n = 8)		
	Control	Per Cent Change NE Alone	Per Cent Change NE + TNG	Control	Per Cent Change NE Alone	Per Cent Change NE + SNP
Mean arterial pressure (torr)	81 ± 2	+22 ± 3*	−4 ± 3	82 ± 2	+20 ± 3*	−4 ± 2
Uterine blood flow (ml/min)	352 ± 14	−39 ± 4*	−23 ± 4*†	349 ± 18	−41 ± 4*	−26 ± 4*†
Uterine vascular conductance (ml/min/torr)	4.4 ± 0.2	−49 ± 4*	−21 ± 4*†	4.3 ± 0.3	−50 ± 5*	−23 ± 5*†
Pulse rate (beats/min)	115 ± 6	−27 ± 3*	+7 ± 5	116 ± 6	−25 ± 5%	+11 ± 7

* $P < 0.05$, values of variables versus control levels.
† $P < 0.05$, uterine blood flow and uterine vascular conductance values during control of hypertension with TNG and SNP versus respective values during infusion of NE alone.

in UBF, whereas SNP preserved but did not increase UBF. Neither agent appeared to harm the fetus. Their data show that when infused to control hypertension, neither agent shunted blood flow away from the uterine vascular bed.

Due to the slow onset of action, the use of hydralazine negates rapid, precise control of hypertension. In addition, the long duration of effect may instigate hypotension should significant hemorrhage occur during cesarean section. When used with continuous blood pressure monitoring, SNP allows fine control of maternal hypertension. However, there is concern about the metabolic effects of cyanide, which has been found in the ovine fetus during maternal exposure to SNP.[6] Trimethaphan effectively controls the hypertension of severe preeclampsia but produces widespread autonomic effects and may prolong the action of succinylcholine.[7]

Our clinical experience with TNG indicates that it may be a promising agent for use during general anesthesia for cesarean section.[8] Its rapid onset of action and short duration of effect allow precise control of hypertension before and during cesarean section. With a molecular weight of 227, TNG will rapidly cross the placenta, but we have found neonatal blood pressures to be normal when infants are placed in the usual head-down position. Since the primary objective of this study was to compare the uterine vascular effects of TNG with those of a commonly used agent, the fetal effects of TNG were not investigated, because chorioamnionitis and premature labor frequently occur after fetal cannulation. The chance of these problems increases with time after preparatory surgery, and in this laboratory a minimum of three and in some cases six or seven days is needed after the surgical procedure for recovery of the manipulated uterine artery.

In awake gravid ewes, TNG and SNP tended to increase UVC when infused alone to decrease MAP by approximately 20 per cent (table 1). Uterine vascular conductance is the reciprocal of resistance and defines the conducting property of the uterine vascular bed. To calculate UVC, the uterine venous pressure must be known. Our method of estimating UVC without including uterine venous pressure has been found in this laboratory to correlate very well with true measurements of UVC. An increase in UVC from control values indicates the occurrence of uterine arterial vasodilatation; a decrease in UVC indicates vasoconstriction. Although the uterine vasodilatation produced by TNG or SNP alone was not statistically significant, this finding suggests that the uterine arteries were not maximally dilated in our awake, undisturbed preparation, and that the effect of such agents on UBF depends not only upon changes in MAP but also upon changes in UVC, or resistance.

Instead of phenylephrine, we selected norepinephrine as the vasopressor, because it is a naturally occurring catecholamine, and it might produce a more clinically relevant model of hypertension. However, this type of model may not accurately represent the chronic, complex cardiovascular alterations of preeclampsia regardless of the vasopressor. As a result of alphaadrenergic stimulation,[9] NE markedly decreased UVC and UBF when it was given alone for 2-min intervals or continuously (fig. 2; table 2). The decreases in UVC were proportionately greater than the respective increases in MAP, which suggests that the vasoconstriction in the uterine vascular bed exceeded that in the total peripheral vasculature.[10] This greater sensitivity of the uterine vasculature to alphaadrenergic stimulation was clearly demonstrated in some ewes when NE produced marked decreases in UVC and UBF but was not associated with changes in MAP and pulse rate.

When infused to prevent or to treat hypertension induced by NE, TNG and SNP promoted uterine vasodilatation and increased UBF (fig. 2; table 2). As a result, neither agent was associated with shunting of blood flow from the uterine vasculature, and they par-

tially protected the uterine vascular bed from the vasoconstrictive effect of NE. Although TNG has a more predominant venodilator effect, our data show that when TNG and SNP were given to produce nearly equal reductions in blood pressure, the vasodilator effects of the two agents on uterine arterial beds were quite similar. One concern about the use of TNG in hypertensive parturients might be that since there is a reduced intravascular volume during preeclampsia,[4] the venodilating properties of TNG may cause a significant decrease in right atrial venous return. However, our clinical experience indicates that although central venous pressure is decreased by TNG, it does not fall to very low levels when mothers are positioned in slight Trendelenburg position with a left lateral tilt.

While caution must be exercised in extrapolating data from artificially hypertensive gravid ewes to patients with hypertension of pregnancy, we believe that the following conclusions are valid. The effect of TNG or SNP on UBF depends not only upon changes in MAP but also upon the extent of uterine vasodilatation occurring during drug administration. When given in equipotent doses to equally prevent or treat hypertension induced by norepinephrine, TNG and SNP antagonize to similar extents the deleterious effect of norepinephrine on the uterine vasculature. As a result, they maintain or improve uterine perfusion and do not cause an extrauterine shunt of blood flow in hypertensive preparations. Both nitroglycerin and nitroprusside allow precise control of maternal hypertension. Since there is concern about the neonatal metabolic effect of nitroprusside (cyanide), the use of nitroglycerin may be a good alternative for controlling maternal hypertension during general anesthesia for cesarean section. However, the fetal effects of nitroglycerin are unknown, and warrant investigation.

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