

## Comparison of Nitroprusside and Hydralazine in Isolated Uterine Arteries from Pregnant and Nonpregnant Patients

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The purpose of the present study was to determine the relative potency of nitroprusside and hydralazine with respect to inhibition of norepinephrine-induced contraction of isolated, uterine arteries from pregnant and nonpregnant patients. The arteries, obtained after hysterectomy, were dissected free from surrounding tissue, and arterial rings were prepared and mounted in tissue chambers filled with Krebs's-bicarbonate solution. Isometric tension was recorded. At concentrations of  $10^{-9}$  M to  $10^{-5}$  M, both nitroprusside and hydralazine produced concentration-dependent inhibition of the contractile response to norepinephrine. Nitroprusside and hydralazine were more potent in relaxing arteries contracted by a lower concentration ( $3 \times 10^{-6}$  M) of norepinephrine than by a higher concentration ( $10^{-5}$  M) of norepinephrine. Regardless of the concentration of norepinephrine, nitroprusside was considerably more potent than hydralazine. The concentrations of nitroprusside that produced 50% inhibition ( $IC_{50}$ ) of the contractile response to norepinephrine ( $3 \times 10^{-6}$  M) in uterine arteries from pregnant and nonpregnant patients were  $3.2 \pm 0.5 \times 10^{-9}$  M ( $n = 5$ ) and  $1.2 \pm 0.1 \times 10^{-9}$  M ( $n = 6$ ), respectively. The  $IC_{50}$  values for hydralazine acting against norepinephrine ( $3 \times 10^{-6}$  M) in the uterine arteries from pregnant and nonpregnant patients were  $5.1 \pm 0.5 \times 10^{-7}$  M ( $n = 5$ ) and  $4.0 \pm 0.5 \times 10^{-7}$  M ( $n = 6$ ), respectively. Nitroprusside ( $10^{-6}$  M), compared to hydralazine ( $10^{-5}$  M), produced the greater maximal inhibition of norepinephrine-induced contraction. The results demonstrate that, although both nitroprusside and hydralazine inhibit norepinephrine-induced uterine artery contraction, nitroprusside has a greater potency compared to hydralazine in producing direct vasodilation of the uterine arteries from pregnant and nonpregnant humans. (Key words: Anesthesia, obstetric. Arteries, uterine: blood flow; pregnant; nonpregnant. Uterus, blood flow: hydralazine; nitroprusside.)

A HYPERTENSIVE EMERGENCY during pregnancy requires immediate intervention to reduce maternal blood pressure. Unfortunately, such a drug-induced lowering of maternal blood pressure usually is associated with a decreased utero-placental perfusion that compromises the fetus. Thus, it would be of interest to find drugs that lower maternal blood pressure and also dilate the uterine vasculature so that perfusion of the

fetus can be maintained, despite the fall in maternal blood pressure.

Hydralazine has been used extensively in the treatment of hypertension complicating pregnancy. However, the relatively slow onset and its comparatively low potency limit its use in hypertensive emergencies of pregnancy.<sup>1</sup> Nitroprusside has had limited use in the treatment of hypertensive emergencies of pregnancies, although the almost immediate onset of action would suggest that nitroprusside should be used in these hypertensive emergencies. Recently, the use of nitroprusside has been reported in a few cases involving pregnant women having surgery for cerebral aneurysm<sup>2,3</sup> or having severe preeclampsia at the time of delivery.<sup>4,5</sup> Except in one report,<sup>4</sup> there were no adverse fetal effects with the use of nitroprusside to lower maternal blood pressure.

There is evidence from both *in vivo* and *in vitro* studies showing that blood vessels from different vascular beds and from various species exhibit marked differences in their responsiveness to nitroprusside and hydralazine. For example, nitroprusside has been shown to be a potent relaxant of preparations of vascular smooth muscle with a predominant tonic (sustained) response to norepinephrine (*e.g.*, rat aorta); whereas, in preparations with phasic (oscillatory) contractility (*e.g.*, rat portal vein) nitroprusside is less effective as a relaxant.<sup>6</sup> Hydralazine has been shown to be a potent relaxant in the human digital artery,<sup>7</sup> the rabbit renal artery,<sup>8</sup> and the rat tail artery.<sup>9</sup> However, in the rabbit and rat aortae contracted by norepinephrine, hydralazine, at concentrations as high as  $10^{-3}$  M, produces only a minor degree of relaxation.<sup>8,10</sup>

Because of the variability in potency of nitroprusside and hydralazine in different vascular beds and in different species, the present study was undertaken to compare the potency of these two drugs in isolated, suffused uterine arteries from humans. The results show that both nitroprusside and hydralazine produce vasodilation in the human uterine artery, and that nitroprusside is considerably more potent than hydralazine in uterine arteries from both pregnant and nonpregnant patients.

### Materials and Methods

Specimens of the ascending branch of the uterine artery were obtained from patients undergoing hysterectomy for various medical reasons. (Use of uterine arter-

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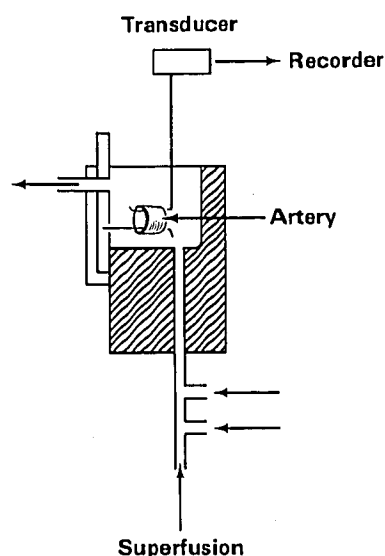


FIG. 1. Schematic drawing of the suffusion system. The fluid with and without drugs was continuously pumped in through the channel in the lower part of the bath and out through the channel in the upper part of the bath. See text for additional details.

ies from patients undergoing hysterectomy was approved by the Institutional Review Board for the University of Texas Medical Branch, Galveston, Texas). The nonpregnant patients varied in age from 23 to 52 years, and were in different phases of the menstrual cycle. The phase (follicular or luteal) of the cycle was determined by the date of the last menstrual period. The pregnant patients varied in age from 20 to 36 years. The length of gestation was full-term.

The mean arterial pressure of the nonpregnant patients was  $105 \pm 8$  mmHg (range, 95–111 mmHg;  $n = 14$ ). The mean arterial pressure of the pregnant patients was  $92 \pm 2$  mmHg (range, 85–102 mmHg;  $n = 5$ ). The patients with a mean arterial pressure within these ranges, and with a diastolic pressure of less than 90 mmHg were considered normotensive. The nonpregnant patients received diazepam, morphine sulfate, and atropine, scopolamine, or glycopyrrolate for preanesthetic medication. Anesthesia was induced with thiopental and maintained with nitrous oxide-oxygen and either halothane, enflurane, or isoflurane. It is recognized that some of these anesthetic-related drugs have prolonged vascular actions, but it was assumed that continuous suffusion of the tissue preparations would remove most of the drugs. Furthermore, the fact that the contractile responses to norepinephrine (NE) did not change during the experiments implies either that the anesthetic-related drugs were washed out before commencement of the experiment or that any residual effects of the drugs did not affect the contractile responses to NE.

Immediately after hysterectomy, sections of the uterus containing the uterine arteries were placed in gassed (95%  $O_2$  and 5%  $CO_2$ ) Krebs-bicarbonate solu-

tion and taken to the laboratory. The preparation of isolated arterial rings and the suffusion techniques used have been described in detail previously.<sup>11,12</sup> The uterine artery was dissected from the tissue sections and divided into four ring preparations with an outer diameter of 2 to 3 mm, and a width of about 2 mm. Either immediately or, in some cases, after storage overnight at 4° C, each ring was mounted between two tungsten, 0.5-gauge wires, one of which was attached to the chamber wall and the other attached to a force-displacement transducer, in a 5-ml volume chamber (fig. 1). Preparations stored for 24 h at 4° C and those mounted and studied immediately after surgery did not differ in their responses to NE.

After the arteries were mounted in the chambers, they were suffused continuously with gassed (95%  $O_2$  and 5%  $CO_2$ ) Krebs-bicarbonate solution at a flow rate of 4 ml/min delivered by a peristaltic pump (Gilson Instruments). The Krebs-bicarbonate solution had the following composition (mM): NaCl, 119;  $NaHCO_3$ , 25; KCl, 3.6;  $MgSO_4$ , 1.2;  $KH_2PO_4$ , 1.2;  $CaCl_2$ , 2.0; glucose, 11; ascorbic acid, 0.005; and disodium ethylenediaminetetraacetate, 0.03. The solution was maintained at 37° C and had a pH of 7.4. The drugs were administered in the inflowing suffusion fluid.

Changes in isometric tension were measured by means of a force-displacement transducer (Statham®) which was connected to the upper wire and recorded on a Gould® recorder (2400 Brush Model) or on a MFE® recorder (2100 Series).

The preparation was allowed a stabilization period of 1 to 2 hr before the experiment began. During that time, basal tension was adjusted repeatedly until the resting tension became stable at 1 g. (One gram has been found to be the optimal resting tension for the human uterine arteries, [unpublished data]). After this stabilization period, the contractile responses to NE, at various concentrations, were reproducible for several hours.

The effects of nitroprusside or hydralazine on NE-induced contraction were determined in two different ways. One of the procedures involved the determination of the inhibitory effectiveness of nitroprusside or hydralazine on arteries that were contracted by prior administration of NE ( $3 \times 10^{-6}$  M or  $10^{-5}$  M) to the suffusion medium. When the contractile response to NE was stable, nitroprusside or hydralazine, at a given concentration or at increasing concentrations, then was added to the precontracted artery. Each concentration of nitroprusside or hydralazine was administered for 15 to 20 min.

In other experiments, after a control cumulative concentration-contractile response curve to NE had been

obtained, the preparation was washed until the baseline tension was regained, and then a further 20-min rest period was allowed. The tissue then was suffused with a given concentration of nitroprusside or hydralazine for 30 min, after which time a second cumulative concentration-response curve with NE was obtained. The same procedure was followed to produce a third concentration-effect curve with NE in the presence of a larger concentration of nitroprusside or hydralazine. Control experiments were performed using the same protocols, but omitting nitroprusside or hydralazine.

All stock solutions and serial dilutions made in Krebs's-bicarbonate solution were prepared shortly before the start of each of the experiments. Thus, the consequences of the fact that hydralazine may be unstable in the bath medium<sup>13</sup> was minimized.

NE-induced tonic contraction in the uterine arteries often was associated with phasic contractions (drug-induced oscillatory activity). When NE-induced oscillatory activity occurred, the lowest tension developed during the rhythmic activity was taken as the response, *i.e.*, the amplitude of the rhythmic activities was not included in the measurements. The concentrations of nitroprusside or hydralazine that inhibited 50% of the responses to NE at a given concentration ( $IC_{50}$ ) were derived by fitting a quadratic equation to the observed data points that were closest to 50%. Mean values in this paper were given, along with standard errors of the mean ( $\pm$ SEM).

Results were analyzed using a nonparametric analysis of variance test (Kruskal-Wallis) to compare three treatment groups: Group 1, nonpregnant, nitroprusside, NE ( $3 \times 10^{-6}$  M); Group 2, nonpregnant, nitroprusside, NE ( $10^{-5}$  M); and Group 3, pregnant, nitroprusside, NE ( $3 \times 10^{-6}$  M). A non-parametric mean separation test was used to determine specific differences in treatment. Results also were analyzed using a nonparametric test (Wilcoxon) to compare Group 1 with treatment Group 4 (nonpregnant, hydralazine, NE [ $3 \times 10^{-6}$  M]); Group 4 with treatment Group 5 (pregnant, hydralazine, NE [ $3 \times 10^{-6}$  M]); treatment Group 6 (follicular, nitroprusside, NE [ $3 \times 10^{-6}$  M]) with treatment Group 7 (luteal, nitroprusside, NE [ $3 \times 10^{-6}$  M]); treatment Group 8 (follicular, hydralazine, NE [ $3 \times 10^{-6}$  M]) with treatment Group 9 (luteal, hydralazine, NE [ $3 \times 10^{-6}$  M]); and treatment Group 10 (follicular, nitroprusside, NE [ $10^{-5}$  M]) with treatment Group 11 (luteal, nitroprusside, NE [ $10^{-5}$  M]). A *P* value less than 0.01 was considered significant.

The following drugs were used: (-)-arterenol bitartrate (Sigma Chemical Company, St. Louis, MO); sodium nitroprusside (Sigma Chemical Company); and hydralazine hydrochloride (Sigma Chemical Company).

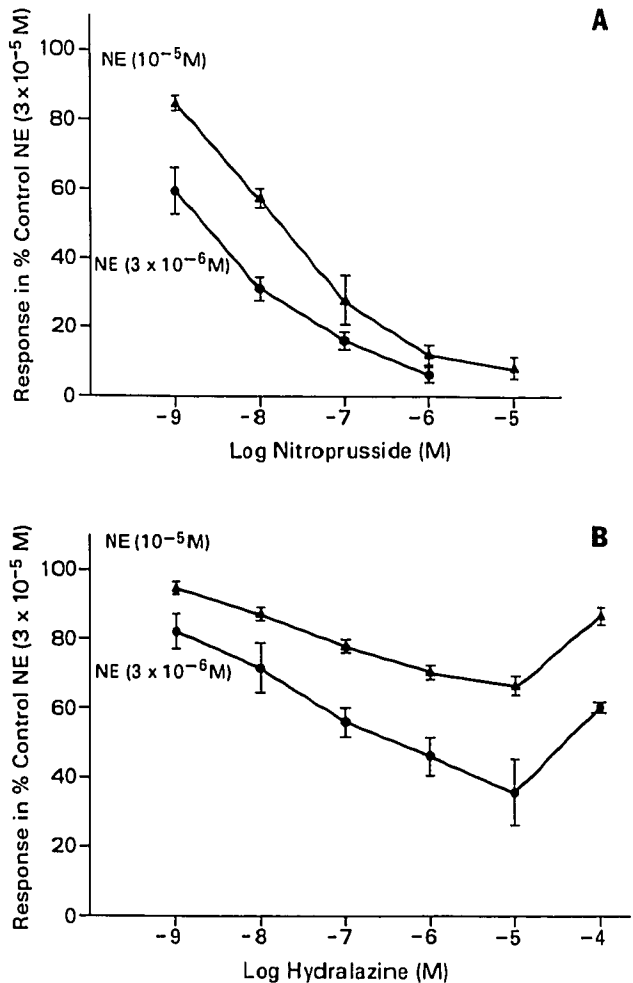


FIG. 2. Relaxant effect of increasing concentrations of nitroprusside (A) and hydralazine (B) on rings of human uterine arteries contracted by NE  $3 \times 10^{-6}$  M ( $\bullet$ ) and NE  $10^{-5}$  M ( $\blacktriangle$ ). Time of exposure to nitroprusside or hydralazine at each concentration was 15 min. Vertical bars represent the SEM of six experiments on arterial rings from six different patients. The curves were significantly different ( $P < 0.05$ ) at each point on the curves.

## Results

### RESPONSIVENESS OF UTERINE ARTERIAL RINGS FROM NONPREGNANT PATIENTS TO NITROPRUSSIDE AND HYDRALAZINE

When the arteries were mounted in the perfusion chamber and the resting tension was applied, there was a temporary increase in tension for about 15 min, followed by a gradual decrease in tension that often was associated with some spontaneous contractile activity. After about 1 hr, the tension was readjusted to 1 g. The tension then remained stable and, as a general rule, no spontaneous contractile activity occurred. In these ar-

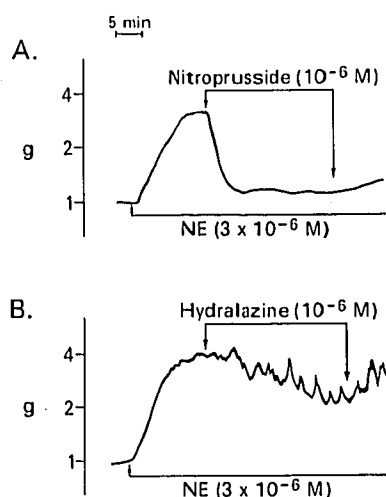


FIG. 3. Inhibition by nitroprusside and hydralazine of NE-induced contractions of the uterine artery from a non-pregnant patient. NE ( $3 \times 10^{-6}$  M) was administered for 15 min before nitroprusside (A) or hydralazine (B) was administered. Each drug was examined on a different arterial ring from the same uterine artery. Note the slow onset of action of hydralazine compared to nitroprusside. Also note the phasic contractions (drug-induced oscillatory contractions) in (B). Phasic contractile activity occurred in about 90% of the arterial rings used to test nitroprusside and hydralazine.

teries with no apparent active tone, administration of nitroprusside ( $10^{-9}$ – $10^{-6}$  M) ( $n = 3$ ) or hydralazine ( $10^{-9}$ – $10^{-6}$  M) ( $n = 3$ ) had no effect on the resting tension.

The potency of nitroprusside or hydralazine to induce relaxation of arteries precontracted with NE was dependent on the concentration of NE used to induce contraction of the uterine arteries. Figures 2A and B show that both nitroprusside and hydralazine were more potent when acting against NE ( $3 \times 10^{-6}$  M, approximately the concentration of NE that produces about 60% of the maximal response to NE),<sup>12</sup> than against NE ( $10^{-5}$  M) ( $P < 0.004$ ). However, at each concentration of NE, nitroprusside was more potent than hydralazine ( $P < 0.008$ ) in inhibiting 50% of the NE-induced contraction ( $IC_{50}$ ). The  $IC_{50}$  values for nitroprusside and hydralazine acting against NE ( $3 \times 10^{-6}$  M) were  $1.2 \pm 0.1 \times 10^{-9}$  M ( $n = 6$ ) and  $4.0 \pm 0.5 \times 10^{-7}$  M ( $n = 6$ ), respectively. The  $IC_{50}$  value for nitroprusside acting against NE ( $10^{-5}$  M) was  $1.4 \pm 0.3 \times 10^{-8}$  M ( $n = 7$ ); hydralazine generally did not inhibit 50% of the response of NE ( $10^{-5}$  M). There was no significant difference ( $P > 0.05$ ) in the  $IC_{50}$  values of nitroprusside acting against NE ( $3 \times 10^{-6}$  M or  $10^{-5}$  M) or hydralazine acting against NE ( $3 \times 10^{-6}$  M) in arteries from patients in the follicular ( $n = 6$ ) or the luteal ( $n = 6$ ) phase of the menstrual cycle. Nitroprusside produced a greater maximal inhibition of NE-induced contraction than did hydralazine. When acting against NE ( $3 \times 10^{-6}$  M), nitroprusside at  $10^{-6}$  M produced  $94 \pm 2\%$  ( $n = 6$ ) inhibition; when acting against NE ( $10^{-5}$  M), nitroprusside at  $10^{-5}$  M produced  $92 \pm 3\%$ , ( $n = 6$ ) inhibition (fig. 2A). The maximal inhibitions of the contractile responses to NE ( $3 \times 10^{-6}$  M) and NE ( $10^{-5}$  M) produced by hydral-

azine ( $10^{-5}$  M) were  $64 \pm 9\%$  ( $n = 6$ ) and  $34 \pm 5\%$  ( $n = 6$ ), respectively. At high concentrations ( $10^{-4}$  M), hydralazine did not produce as great an inhibition as that produced by  $10^{-5}$  M hydralazine (fig. 2B).

Nitroprusside ( $10^{-6}$  M), when added to an artery precontracted with NE, produced relaxation that appeared more rapid in onset (fig. 3A) than that following hydralazine ( $10^{-6}$  M) (fig. 3B). In the concentration-effect experiments (figs. 2A and 2B), a steady-state relaxation of NE-induced contraction occurred within 3 to 8 min at each concentration of nitroprusside ( $n = 13$ ), whereas the steady-state relaxation developed more slowly (15–20 min) at each concentration of hydralazine ( $n = 12$ ). Furthermore, it should be noted that with equiactive concentrations ( $IC_{50}$ ) of nitroprusside and hydralazine, nitroprusside had a faster onset of action than did hydralazine ( $n = 3$ ).

#### CONCENTRATION-CONTRACTILE RESPONSE CURVES FOR NE IN THE PRESENCE OF NITROPRUSSIDE OR HYDRALAZINE

Concentration-contractile response curves for NE in uterine arterial rings from nonpregnant patients were recorded in the absence and presence of nitroprusside or hydralazine. Both nitroprusside ( $10^{-8}$  M– $10^{-6}$  M) and hydralazine ( $10^{-8}$  M– $10^{-6}$  M) caused shifts to the right of the log concentration-response curves to NE and reduced the maximal response to NE ( $3 \times 10^{-5}$  M). The influences of nitroprusside ( $10^{-7}$  M) or hydralazine ( $10^{-7}$  M) are shown in figures 4 and 5, respectively. The maximal contractile response to NE ( $3 \times 10^{-5}$  M) in the presence of nitroprusside ( $10^{-7}$  M) or hydralazine ( $10^{-7}$  M) was depressed by  $58 \pm 9.5\%$  ( $n = 5$ ) and  $18 \pm 2.9\%$  ( $n = 6$ ), respectively ( $P < 0.01$ ). In the presence of comparable concentrations of nitroprusside ( $10^{-7}$  M) and hydralazine ( $10^{-6}$  M) (*i.e.*, concentrations about one log unit higher than their  $IC_{50}$  values when inhibiting NE [ $3 \times 10^{-6}$  M]), the contraction produced by NE ( $3 \times 10^{-5}$  M) was still significantly ( $P < 0.01$ ) more depressed by nitroprusside than by hydralazine.

#### RESPONSIVENESS OF UTERINE ARTERIAL RINGS FROM PREGNANT PATIENTS TO NITROPRUSSIDE AND HYDRALAZINE

The contractile behavior of uterine arteries from pregnant patients was similar to that of uterine arteries from nonpregnant patients. In agreement with earlier findings, the potency of NE in causing contraction of uterine arteries from pregnant patients was similar to that in uterine arteries from nonpregnant patients.<sup>12</sup> Both nitroprusside ( $10^{-9}$  M– $10^{-5}$  M) and hydralazine ( $10^{-9}$  M– $10^{-5}$  M) produced concentration-dependent inhibition of NE-induced contractions. As observed in the

uterine arteries from nonpregnant patients, the onset of action of nitroprusside appeared to be considerably faster than that of hydralazine. The potencies of nitroprusside or hydralazine in causing inhibition of the NE-induced ( $3 \times 10^{-6}$  M) contractions were not significantly different from those in uterine arteries from nonpregnant patients. However, nitroprusside was significantly more potent than hydralazine ( $P < 0.008$ ) in inhibiting 50% of the NE-induced ( $3 \times 10^{-6}$  M) contraction in uterine arteries from pregnant patients. The  $IC_{50}$  values for nitroprusside and hydralazine were  $3.2 \pm 0.5 \times 10^{-9}$  M ( $n = 5$ ) and  $5.1 \pm 0.5 \times 10^{-7}$  M ( $n = 5$ ), respectively. Also, the maximal inhibitions produced by nitroprusside ( $n = 5$ ) and hydralazine ( $n = 5$ ) when acting against NE ( $3 \times 10^{-6}$  M) were not significantly different from those produced in uterine arteries from nonpregnant patients.

### Discussion

Our results show clearly that there is a marked difference in the vasodilatory potency of nitroprusside and hydralazine on human uterine arteries. However, the potency of nitroprusside or hydralazine on uterine arteries from pregnant patients compared to nonpregnant patients is not significantly different. Nitroprusside is about 100 times more potent than hydralazine in inhibiting the contractile response to NE; and nitroprusside, compared to hydralazine, produces the greater maximal inhibition of NE-induced contraction.

The concentrations of nitroprusside and hydralazine used in these studies to inhibit NE-induced contractions may be in the range of the concentrations of the drugs used clinically in patients to produce hypotension. (It must be emphasized that concentrations of drugs used in studies on isolated smooth muscle preparations cannot be translated without reservation to clinical situations). The average adult dose of nitroprusside is about  $0.1-1.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ .<sup>13</sup> We estimate that the serum concentration of nitroprusside in a 70-kg patient could be in the order of  $0.003 \mu\text{g}/\text{ml}$  (or about  $10^{-9}$  M), if we assume that nitroprusside molecules are not excreted or metabolized and are distributed in all extracellular water. Our  $IC_{50}$  value for nitroprusside of  $1.2 \pm 0.1 \times 10^{-9}$  M in isolated uterine arteries is within this range. The serum levels of hydralazine are in the range of  $10^{-7}$  M to  $10^{-6}$  M at an average therapeutic dose of 50 mg of hydralazine given by mouth.<sup>14</sup> Our  $IC_{50}$  value for hydralazine of  $4.0 \pm 0.5 \times 10^{-7}$  M is also within this range.

We have shown that the effectiveness of nitroprusside or hydralazine to inhibit NE-induced contractions in the human uterine artery is dependent on the concentration of NE used to induce the contraction. A similar influence of NE concentration on the inhibitory effect

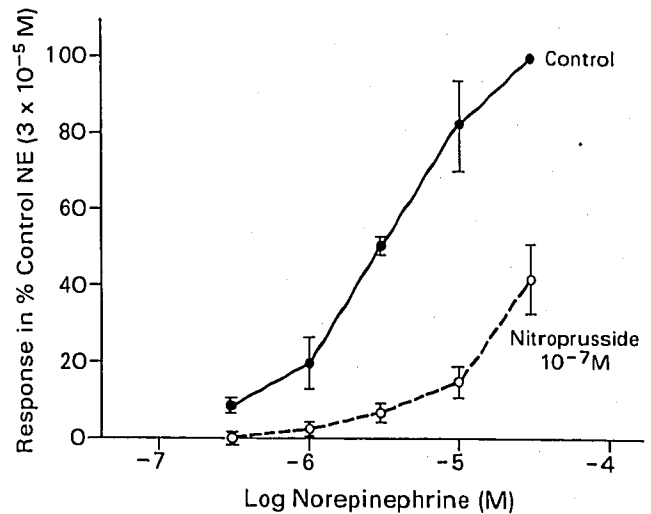


FIG. 4. Log concentration-contraction response curves for norepinephrine (NE) in the human uterine artery preparation in the absence (solid symbols) and in the presence (open symbols) of nitroprusside. After obtaining the control NE concentration-responses, nitroprusside ( $10^{-7}$  M) was administered for 30 min before a subsequent concentration-response curve to NE was determined. Vertical bars represent the SEM of five experiments from five different patients. The curves were significantly different ( $P < 0.01$ ) at each point on the curves.

of nitroprusside has been reported by Karaki *et al.*<sup>15</sup> They showed that the inhibitory effect of nitroprusside on the contractile response to lower concentrations of NE was greater than that obtained at higher concentra-

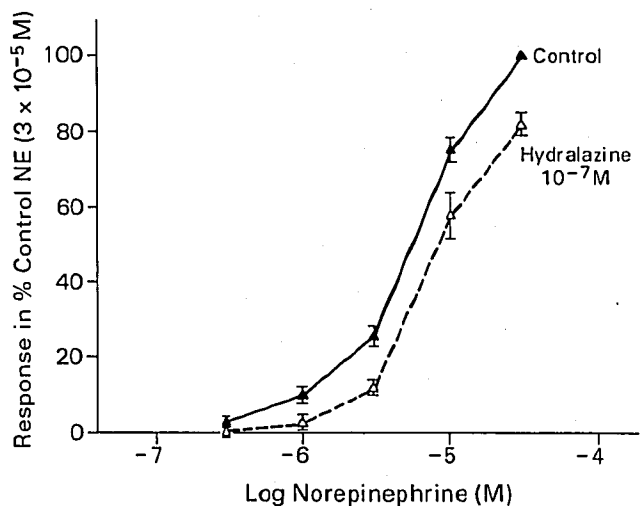


FIG. 5. Log concentration-contraction response curves for norepinephrine (NE) in uterine arteries in the absence (solid symbols) and in the presence (open symbols) of hydralazine. After obtaining the control NE concentration-responses, hydralazine ( $10^{-7}$  M) was administered for 30 min before a subsequent concentration-response curve to NE was determined. Vertical bars represent the SEM of six experiments from six different patients. The curves were significantly different ( $P < 0.01$ ) at each point on the curves.

tions of NE in canine renal arteries. The influence of NE concentration on the inhibitory effect of hydralazine may be involved in the explanation of our results showing that the highest concentration ( $10^{-4}$  M) of hydralazine used in these studies produced less inhibition of the NE-induced contraction than did hydralazine ( $10^{-5}$  M). The fact that hydralazine (at high concentrations) inhibits the enzyme monoamine oxidase<sup>16</sup> and, thus, may effectively increase the concentration of NE in the receptor biophase may explain the decreased inhibitory effectiveness of hydralazine at the higher concentrations used in our study.

Nitroprusside at a given concentration appears to have a more rapid onset of action to inhibit NE-induced contractions than has hydralazine in isolated, suffused uterine arteries from humans. This difference in onset of action is consistent with the difference in the onset of the hypotensive action of these drugs when they are infused into patients. The vasodilatory effect of nitroprusside in patients is seen almost immediately after an infusion is started, whereas the effect of hydralazine develops gradually over 15 to 20 min.<sup>1</sup>

Blood vessels from different vascular beds and from different species have variable sensitivities to nitroprusside and to hydralazine. Our results demonstrate that the human uterine artery is sensitive to a direct vasodilatory effect of these drugs. In fact, as judged by  $IC_{50}$  values, the potency of nitroprusside acting against NE-induced contractions in the uterine artery from humans is greater than the potency of nitroprusside in blood vessels such as the rat tail artery ( $IC_{50} = 3 \times 10^{-7}$  M),<sup>17</sup> the rat thoracic aorta ( $IC_{50} = 3 \times 10^{-8}$  M),<sup>18</sup> the rabbit pulmonary artery ( $IC_{50} = 10^{-6}$  M),<sup>19</sup> and the canine renal artery ( $IC_{50} = 3 \times 10^{-7}$  M to  $10^{-5}$  M).<sup>15</sup> The potency of hydralazine is comparable to that found in other blood vessels sensitive to the vasodilatory effect of hydralazine. For example, the  $IC_{50}$  value for hydralazine is about  $10^{-7}$  M in the rabbit thoracic aorta<sup>20</sup> and the rabbit renal artery.<sup>7</sup>

Pregnancy causes profound changes in the maternal vascular system, especially in the utero-placental vascular bed. Although there is ample evidence showing that the maternal pressor responses to several vasoactive drugs are decreased during pregnancy, the effect of pregnancy on the responsiveness of isolated uterine arteries to vasoactive drugs is not well established. However, we have reported previously that verapamil is significantly more potent in inhibiting NE-induced contraction in isolated uterine arteries from pregnant than from nonpregnant patients, and that there is no significant difference in the concentration of NE that produced 50% of the maximal contractile response to NE in uterine arteries from pregnant and nonpregnant patients.<sup>12</sup> Our present findings that nitroprusside or hy-

dralazine have similar vasodilatory potencies in uterine arteries from pregnant and nonpregnant patients indicate that these drugs may act through mechanisms that are not influenced by pregnancy.

The sensitivity of the isolated uterine artery to nitroprusside and hydralazine may indicate a similar sensitivity of the whole uterine vasculature to nitroprusside and hydralazine. This would be in keeping with the observations of an increased uterine blood flow, despite the decrease in the systemic arterial blood pressure induced by nitroprusside<sup>21,22</sup> and by hydralazine<sup>23,24</sup> in hypertensive pregnant ewes. The high sensitivity of the isolated uterine artery to nitroprusside, however, does contrast with other reports showing that nitroprusside decreased the uterine blood flow in hypertensive pregnant ewes.<sup>24,25</sup> As demonstrated in our studies, the potency of nitroprusside varied with the concentration of NE used to induce contraction. Thus, the experimental conditions (the concentrations of the vasoconstrictor agents and the resultant vasoconstriction) for the studies on the effects of nitroprusside in hypertensive pregnant ewes could explain the different effects of nitroprusside on uterine blood flow. It should be noted that in the studies using isolated uterine arteries from pregnant patients, the  $IC_{50}$  values for nitroprusside and hydralazine were similar to those values found in nonpregnant patients.

Because of the potential for fetal cyanide toxicity,<sup>13,26</sup> nitroprusside has not been used frequently in pregnant patients. However, a few reports of the use of nitroprusside in certain emergencies of pregnancy (*i.e.*, hypertension of preeclampsia and cerebral aneurysm) have appeared.<sup>2-5</sup> Except in one report,<sup>4</sup> there were no adverse fetal effects with the use of nitroprusside to lower maternal blood pressure. Our results showing that nitroprusside is more potent and has a greater efficacy than hydralazine in inhibiting the response to NE in isolated uterine arteries from both pregnant and nonpregnant humans may provide a rationale for the use of nitroprusside in hypertensive emergencies in pregnant patients if standard therapy has failed.

In summary, the results from this study show that both nitroprusside and hydralazine induce dilation of uterine arteries from pregnant and nonpregnant patients, and that nitroprusside is considerably more potent than hydralazine in producing vasodilation. The results support the possibility that in the presence of nitroprusside or hydralazine, uterine perfusion might be maintained as a result of direct vasodilation of the uterine arteries, even though the blood pressure of the mother is lowered.

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