The Vascular Mechanism of Ephedrine’s Beneficial Effect on Uterine Perfusion during Pregnancy

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Sensitivity to the vasoconstricting actions of adrenergic agents is altered during pregnancy and is drug-, regional vascular bed-, and endothelium-dependent. To examine whether the uterine perfusion-sparing property of ephedrine is due to local actions, we examined the effects in vitro of ephedrine and the α-adrenergic agonist metaraminol (10⁻¹⁰–10⁻⁵ M) in uterine and femoral vessels, with and without functional endothelium, from nonpregnant and pregnant ewes. Both agents produced dose-dependent contractions in all vascular rings. In all cases metaraminol was more potent (by analysis of the concentration producing a 50% maximal response [EC₅₀]) and efficacious (by maximal effect). Pregnancy increased constriction from both agents in femoral arterial rings, whereas pregnancy decreased constriction from both agents in uterine arterial rings. However, the ratio of maximal effect at femoral versus uterine rings during pregnancy was greater for ephedrine (5.2 ± 0.6) than metaraminol (1.9 ± 0.3). This difference was further accentuated by endothelium removal. Constriction to both agents was abolished by phentolamine (10⁻⁶ M). These data suggest that both ephedrine and metaraminol constrict uterine and systemic vessels by actions on α-adrenoceptors, and that ephedrine may spare uterine perfusion during pregnancy due to more selective constriction of systemic vessels than that caused by metaraminol. (Key words: Anesthesia: obstetric. Sympathetic nervous system, α-adrenergic agonists: ephedrine; metaraminol. Uterus: blood flow.)

Whether ephedrine is preferred over α-adrenergic agonists as a vasopressor for treatment of intraspinal anesthesia–induced hypotension in obstetrics has recently been questioned. Originally ephedrine was chosen, based on observations in pregnant sheep and baboons of greater improvement in uterine blood flow and less uterine vasoconstriction with ephedrine than with other agents possessing more α-adrenergic activity (e.g., phenylephrine, methoxamine, and metaraminol). The reason for this difference is that ephedrine is believed to increase blood pressure during spinal hypotension primarily by increasing cardiac output, whereas metaraminol increases systemic (and uterine) vascular resistance. This concept has been recently challenged by laboratory and clinical observations. α-Adrenergic agonists may improve uterine perfusion during hypotension by increasing cardiac output, both by direct inotropic effects mediated by α₁ adrenoceptors and by increasing preload, since the sensitivity of veins to α-adrenergic constriction increases during pregnancy. Clinical observations suggest that phenylephrine effectively increases maternal cardiac output during epidural anesthesia-induced hypotension and does not produce detrimental effects in neonatal acid-base status or catecholamines in healthy women.

A complementary explanation, aside from effects on cardiac output, of ephedrine’s superiority in obstetrics may be regional vascular effects: perhaps ephedrine preferentially constricts nonuterine vascular beds. Vascular reactivity to a variety of vasopressors is altered in pregnancy. In general, sensitivity is decreased, but sensitivity to an agent may vary among vascular beds. Global and regional changes in vascular reactivity during pregnancy may be due to changes in receptor number or function, metabolism and clearance of drugs, or altered release of or sensitivity to endothelium-derived relaxing factor or prostaglandins. Previous examinations of vascular sensitivity during pregnancy have used preparations without documented functional endothelium, and have focused on fundamental questions of receptor number or response with other receptors and metabolism specifically inhibited, or have not examined the clinically relevant agent, ephedrine. If, as suggested, preclampsia is associated with diffuse endothelial cell dysfunction, the effect of ephedrine in vessels without endothelium would be of interest.

In this study we examined the constricting effects of ephedrine on uterine and femoral vessels in vitro, including the roles of pregnancy, vascular endothelium, and adrenergic receptors on these effects. These studies were performed without inhibition either of reuptake or metabolism of these agents, or of other receptors (β-adrenergic) upon which they may act, because agents inhibiting reuptake or actions at other receptors would not be administered with a pressor agent in the clinical setting. For comparison, we examined metaraminol, an agent previously examined in this and other laboratories in vivo on the uterine and systemic hemodynamic response to spinal hypotension.

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Materials and Methods

The protocol was approved by the Animal Care and Use Committee.

Vascular Ring Preparation

Uterine and femoral arteries were obtained from pregnant (0.8–0.9 gestation; n = 6) and nonpregnant sheep (n = 7). In vitro vessel preparation has been described in detail elsewhere. In brief, animals were anesthetized with pentobarbital (30 mg/kg intravenously), and cardiac arrest was produced by intravenous injection of saturated KCl solution. Sections of arteries were removed and placed in ice-cold oxygenated modified Krebs-Henseleit solution. Arteries were dissected free of adhesive tissue, cut into 4-mm-wide rings, and mounted, using two stainless steel hooks in tissue chambers in a four- or six-tissue chamber system, filled with Krebs-Henseleit solution gassed with O2–CO2 (95%–5%), pH 7.40, 37°C. In each chamber, one hook was attached to the base of the bath and the other connected to a Grass® 7 PTO3C transducer by 4-0 silk suture. Isometric force was continuously recorded using a Grass model 7 polygraph (Quincy, MA).

For some rings, endothelial cells were removed by gentle rubbing of the intimal surface with stainless steel wire. Functional integrity of endothelium was determined by demonstration of relaxation (minimum 25%) to acetylcholine (10⁻⁷–10⁻⁴ M) following preconstriction with norepinephrine (10⁻⁷ M) and by histologic examination with silver staining. Since others have demonstrated inconsistent responses to acetylcholine in sheep arteries, functional integrity of endothelium was also determined by demonstration of relaxation to bradykinin (10⁻⁸–10⁻⁶ M) following preconstriction with norepinephrine (10⁻⁷ M).

Experimental Protocol

After equilibration for 1 h at 1 g initial tension, rings were stretched and contracted in a stepwise manner to 20 mM KCl until the optimum length–tension (just maximal tension producing a maximal response to KCl) was obtained. Baths were washed free of KCl, and the rings were then equilibrated at this tension for an additional 45 min. To obtain dose–responses, ephedrine or metaraminol was added to the bath in a cumulative manner (10⁻¹⁰–10⁻⁸ M). In pilot studies, maximal effects were obtained at concentrations of 10⁻⁵ M for both ephedrine and metaraminol. In some studies rings were pretreated with indomethacin (10⁻⁵ M) and phenolamine (10⁻⁵). These concentrations have been shown to block prostaglandin- and α-adrenergic–mediated effects, respectively. Pilot studies demonstrated that these agents did not alter resting tension, and that indomethacin alone did not alter the response to ephedrine or metaraminol.

In a separate set of experiments to examine the effects of a peripheral artery of similar size to the uterine artery, distal femoral arteries were obtained from nonpregnant and pregnant ewes. These vessel rings were prepared and studied as described above.

SOLUTION AND DRUGS

Tissue chambers (17 ml) were filled with Krebs-Henseleit solution with composition (millimolar): NaCl 118.3, KCl 4.7, CaCl₂ 2.5, MgSO₄ 1.2, KH₂PO₄ 1.2, NaHCO₃ 25, NaEDTA 0.026, and glucose 11.1. Acetylcholine, bradykinin, ephedrine, epinephrine, metaraminol, and indomethacin were obtained from Sigma Chemical Co. (St. Louis, MO). Phenolamine was obtained from CIBA Geigy (Ardsley, NY). Drugs were dissolved fresh each day in distilled water except for indomethacin, which was dissolved in NaHCO₃ (3 × 10⁻⁵ M), and were added to tissue chambers in volumes ≤ 0.2 ml.

Statistics

Data are expressed as mean ± SEM. Unless otherwise stated, all data describing femoral vessel responses refer to responses in the main femoral artery and not the small distal segments. Since systemic and uterine vessel sensitivities to KCl (as determined by the concentration producing a 50% maximal response [EC₅₀]) do not change during pregnancy, responses to ephedrine and metaraminol were calculated as the percent of response to KCl 20 mM rather than as absolute values per gram vessel weight. EC₅₀ concentrations were calculated by standard methods. Because ephedrine showed a feeble but maximal response in some rings to 10⁻⁴ M but minimal response at 10⁻⁴ M, accurate EC₅₀ concentrations could not be calculated and were assigned a value of > 100 × 10⁻⁶. Groups were compared for EC₅₀ and maximal responses by one-way analysis of variance (ANOVA) and for full dose–response curves by two-way ANOVA for repeated measures followed by Student’s t test with Bonferroni correction. P < 0.05 was considered statistically significant.

Results

Optimum tension was greater for femoral than for uterine rings but was not altered by endothelium removal or pregnancy (table 1). Pregnancy increased KCl-induced tension in uterine rings and decreased KCl-induced tension in femoral rings (table 1), although tension was not corrected in this study for cross-sectional area. Vessel diameters (centimeters) were: nonpregnant uterine artery
0.76 ± 0.08, pregnant uterine artery 1.1 ± 0.03, non-
pregnant femoral artery 1.8 ± 0.03, and pregnant femoral
artery 2.3 ± 0.06. Bradykinin reliably relaxed norepi-
nephrine-contracted rings that had not been rubbed (by
39 ± 4% at 10^{-8} M and 49 ± 3% at 10^{-7} M), but not those
that had been rubbed with stainless steel wire. Similarly,
silver staining demonstrated complete removal of endo-
thelium in rings that had been rubbed with stainless steel
wire, but endothelium was present in rings that had not
been rubbed.

Ephedrine produced dose-dependent contractions in
all vascular rings studied (fig. 1). Endothelium removal
enhanced sensitivity to ephedrine, as determined by EC_{50},
in nonpregnant uterine arteries, decreased sensitivity in
nonpregnant femoral arteries, and did not alter sensitivity
in pregnant arteries (table 2). Maximal response was in-
creased by endothelium removal in nonpregnant femoral
arteries and was decreased in pregnant femoral arteries
(fig. 1, table 2). The effect of pregnancy on vascular re-
response to ephedrine differed between femoral and uterine
vessels. In femoral vessels, pregnancy decreased sensitivity
and increased maximal response, whereas in uterine ves-
sels pregnancy decreased both sensitivity and maximal
response (fig. 1, table 2). Phentolamine completely abol-
ished the response to ephedrine.

Metaraminol produced dose-dependent contractions in
all vascular rings studied (fig. 2). Endothelium removal
enhanced sensitivity to metaraminol in nonpregnant
uterine arteries and decreased sensitivity in pregnant
uterine arteries (table 3). Maximal response was decreased
by endothelium removal in pregnant femoral arteries (ta-
ble 3). The effect of pregnancy on vascular response to
metaraminol was similar to ephedrine. In femoral vessels,
pregnancy decreased sensitivity and increased maximal
response, whereas in uterine vessels, pregnancy decreased
both sensitivity and maximal response (fig. 2, table 3).
Phentolamine abolished the response to metaraminol.

Although the effects of ephedrine and metaraminol
were qualitatively similar, there were several quantitative
differences. In all cases metaraminol was more potent (P
< 0.05; tables 2 and 3) and produced contractions of
greater magnitude than ephedrine. Also, their selectivity
for constriction of femoral versus uterine vessels differed.
When responses of femoral and uterine vascular rings
from nonpregnant animals were compared, both ephed-
rine and metaraminol, over a broad concentration range,
produced approximately equivalent constriction in both
types of rings (figs. 1 and 2). In contrast, a similar com-
parison in rings from pregnant animals showed more
femoral than uterine constriction by each agent. Of par-

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Pregnant</th>
<th>Endothelium</th>
<th>Optimum Tension (g)</th>
<th>KCl-induced Tension (g)</th>
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</thead>
<tbody>
<tr>
<td>Femoral</td>
<td>No</td>
<td>Yes</td>
<td>13.7 ± 0.3</td>
<td>9.1 ± 1.3</td>
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<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>13.2 ± 0.6</td>
<td>5.1 ± 0.6*</td>
</tr>
<tr>
<td>Femoral</td>
<td>Yes</td>
<td>Yes</td>
<td>13.9 ± 0.2</td>
<td>4.1 ± 0.3*</td>
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<tr>
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<td>No</td>
<td>Yes</td>
<td>13.8 ± 0.2</td>
<td>5.6 ± 0.4*</td>
</tr>
<tr>
<td>Uterine</td>
<td>No</td>
<td>Yes</td>
<td>9.6 ± 0.2</td>
<td>4.3 ± 0.5</td>
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<td>Yes</td>
<td>No</td>
<td>10.0 ± 0.4</td>
<td>6.3 ± 0.9*</td>
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<tr>
<td>Uterine</td>
<td>Yes</td>
<td>Yes</td>
<td>10.2 ± 0.2</td>
<td>12.8 ± 3.7†</td>
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<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>10.5 ± 0.3</td>
<td>12.7 ± 1.7**†</td>
</tr>
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</table>

* * P < 0.05 versus endothelium-intact rings.  † P < 0.05 versus nonpregnant rings.

Fig. 1. Effects of ephedrine. Contraction, expressed as percent KCl
response in uterine (top) and femoral (bottom) rings with functional en-
dothelium from nonpregnant (circles) and pregnant (squares) animals.
* P < 0.05; dose-response curves differ between nonpregnant and
pregnant rings in both vessel types by two-way ANOVA (see table 2
for additional comparisons).
ephedrine for femoral versus uterine constriction was greater during pregnancy than that of metaraminol (femoral/uterine response over $10^{-7}$–$10^{-3}$ M was 2.5–6.8 for ephedrine vs. 1.9–3.3 for metaraminol, and maximal response ratio was 5.2 ± 0.6 for ephedrine vs. 1.9 ± 0.3 for metaraminol; $P < 0.05$). This difference was enhanced by endothelium removal (femoral/uterine response over $10^{-7}$–$10^{-3}$ M was 3.2–10.7 for ephedrine vs. 1.1–2.1 for metaraminol, and maximal response ratio was 3.1 ± 0.3 for ephedrine vs. 1.1 ± 0.2 for metaraminol; $P < 0.05$).

Examination of the smaller distal femoral arterial rings (diameter of nonpregnant rings 0.84 ± 0.02 cm and of pregnant rings 0.96 ± 0.04 cm) were similar to the larger main femoral arterial rings. Specifically, $EC_{50}$ values in rings with and without endothelium and from nonpregnant and pregnant ewes for both ephedrine and metaraminol did not differ between small and large femoral rings. Maximal responses to both ephedrine and metaraminol were greater in small than in large femoral rings with functional endothelium from nonpregnant animals. For ephedrine, maximal response (percent of KCl response) was 182 ± 26% in small versus 89 ± 13% in large femoral rings ($P < 0.05$) and for metaraminol maximal response was 511 ± 45% in small versus 194 ± 37% in large femoral rings ($P < 0.05$). However, in rings with functional endothelium from pregnant animals, the maximal response to ephedrine and metaraminol did not differ between small and large femoral vessels. Just as with the large rings, selectivity for distal femoral versus uterine constriction was greater during pregnancy for ephedrine (5.3 ± 0.5) than for metaraminol (1.8 ± 0.4; $P < 0.05$). These selectivity ratios are within 5% of those obtained using the larger main femoral arterial rings in the comparison.

**Discussion**

In general, pregnancy is believed to be associated with a refractoriness to vasoconstriction from adrenergic agonists. Initial studies examining pressor responses following intravenous administration demonstrated refractoriness to norepinephrine and phenylephrine in ewes. Results in humans have been more conflicting, with a diminished, unchanged, or increased response to norepinephrine during pregnancy (for discussion, see McLaughlin et al.). Unfortunately, changes in baroreflex responses, differences in effect on cardiac output of these
Table 3. Metaraminol's Effect in Rings With and Without Endothelium

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Pregnant</th>
<th>Endothelium</th>
<th>Maximum Tension (% response to KCl)</th>
<th>EC50 × 10^-6 M</th>
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</thead>
<tbody>
<tr>
<td>Femoral</td>
<td>No</td>
<td>Yes</td>
<td>194 ± 37</td>
<td>1.4 ± 0.2</td>
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<td></td>
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<td>242 ± 40</td>
<td>1.6 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>362 ± 43*</td>
<td>3.2 ± 0.5*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>236 ± 22†</td>
<td>3.2 ± 1.2</td>
</tr>
<tr>
<td>Uterine</td>
<td>No</td>
<td>Yes</td>
<td>223 ± 30</td>
<td>4.8 ± 0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>245 ± 24</td>
<td>1.7 ± 0.5†</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>169 ± 10*</td>
<td>8.6 ± 1.7*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>197 ± 41</td>
<td>12.2 ± 1.9**†</td>
</tr>
</tbody>
</table>

* P < 0.05 versus nonpregnant rings.
† P < 0.05 versus endothelium intact rings.

of in vitro vascular responses during pregnancy with other α-adrenergic agonists. First, our data with ephedrine and metaraminol agree with previous in vivo studies demonstrating decreased sensitivity in systemic and uterine vessels to α-adrenergic agonists during pregnancy.6

Second, alteration in clearance of adrenergic agents may explain the discrepancy between our results and other in vitro studies. For example, we observed diminished sensitivity to adrenergic agonists in systemic vessels in this study, in which catecholamine reuptake and metabolism were not blocked, whereas when blockers of catecholamine reuptake and metabolism have been included, others have reported no change in response to norepinephrine during pregnancy.5 Altered reuptake may also explain why sensitivity to phenylephrine in vitro is increased when such blockers are not included.17 That regional differences (uterine vs. carotid) in vascular sensitivity still exist in the presence of these blockers suggests that catecholamine reuptake and metabolism may vary with vascular bed or that other factors are involved.

Endothelium-released vasoactive factors are important in regional vascular action of drugs and may be important in physiologic changes in pregnancy and pathophysiologic changes in preeclampsia.12 The regional vascular and drug-dependent differences in the effect of endothelium removal on vasoconstrictor responses are consistent with local and receptor-specific mediated differences. Of particular relevance are the observations that pregnancy is associated with increased release of endothelium-derived relaxing factor by provocative stimuli9 and that preeclampsia is associated with evidence of endothelial cell dysfunction.12 Such dysfunction may explain in part the increased sensitivity to vasopressors in preeclampsia, and one could speculate that diminished sparing of uterine constriction observed after endothelium removal in this study may be reflected in diminished sparing of uterine perfusion with administration of these agents in the clinical setting. If this is the case, ephedrine is to be even more preferred over α-adrenergic agonists in women with pre-
eclampsia, because selectivity is almost completely lost to the \(\alpha_1\)-adrenergic agonist, metaraminol, but not to ephedrine.

Increased maximal response during pregnancy to both ephedrine and metaraminol in femoral arteries is consistent with similar observations in rats with norepinephrine. This difference is not likely due to changes in \(\alpha_1\) adrenoceptor number in systemic vessels. Similarly, whether the diminished relative effect in uterine vessels during pregnancy for ephedrine in comparison with metaraminol is due to alteration in \(\alpha_2\)-adrenoceptor density, as has been demonstrated in myometrium, or some other factor is not known. A more complete understanding of the cause(s) for ephedrine’s increased selectivity is central to the design and selection of better vasoressors for use in pregnancy.

This study compared uterine vascular responses to only one systemic vessel (femoral artery) for two reasons. First, because alteration in the relative roles of neuronal and nonneuronal catecholamine reuptake varies with vessel size and type, it is important to compare vessels of similar size and type. Since similar results were obtained in large and small femoral vessels, differences in size between femoral and uterine vessels is unlikely to explain differences in drug potencies observed or the effect of pregnancy. Although we did not correct for cross-sectional area or weight in this study, all effects were compared to contraction to KCl, such that identical results would have been obtained had such a conversion been performed. Second, although vascular reactivity to pressor agents varies with regional bed, the most relevant to support blood pressure during regional anesthesia-induced hypotension is the musculoskeletal bed, which should be well represented by the femoral artery.

Finally, the authors acknowledge that the clinical relevance of these in vitro data from sheep is far from certain. Nonetheless, there is an excellent agreement between responses in vitro to metaraminol and ephedrine in uterine artery rings from sheep and human, and the \(EC_{90}\) data in this study agree well with previous examinations in sheep. Whereas metaraminol is not a commonly used vasopressor clinically, its uterine effects during pregnancy have been compared to ephedrine extensively in laboratory animals, and it is representative of a relatively pure \(\alpha_1\)-adrenergic agonist. Although even \(EC_{90}\) concentrations would be unlikely to be sustained clinically, maximal concentrations immediately following a bolus may approach \(10^{-6}\) \(M\), assuming initial distribution restricted to the vascular space. However, differences in sensitivity probably exist between the in vitro and in vivo situations, due to reflex responses and luminal versus extraluminal effects, and relative potencies were maintained at concentrations less than \(EC_{90}\). In making potency and efficacy comparisons, we disregarded the 10-fold difference in clinically used doses of these agents. However, correctins for this by comparing effects of ephedrine to those of metaraminol, an order of magnitude less, do not alter the conclusions.

In summary, the vasoconstrictor actions of both ephedrine and metaraminol in vitro are altered by the presence of functional endothelium, the regional vascular bed, and pregnancy. Metaraminol is a more potent and effective vasoconstrictor, and during pregnancy, is less selective for femoral over uterine vessels than ephedrine. Such selectivity is abolished by endothelium removal for metaraminol, yet ephedrine retains more constriction in femoral than in uterine vessels. These results support the uterine-perfusion sparing property of ephedrine and provide a rationale for examining the cause(s) of this effect.

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