Nitric oxide activity in the peripheral vasculature during normotensive and preeclamptic pregnancy

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Nitric oxide activity in the peripheral vasculature during normotensive and preeclamptic pregnancy. Am. J. Physiol. 277 (Heart Circ. Physiol. 46): H848–H854, 1999.—We investigated the role of nitric oxide (NO) in the vascular resistance changes of normotensive and preeclamptic pregnancy. Forearm blood flow (FBF) responses to brachial artery infusion of N³-monomethyl-L-arginine (L-NMMA), an NO synthase inhibitor, and angiotensin II (ANG II), an NO-independent vasoconstrictor, were determined by plethysmography in 20 nonpregnant women, 20 normotensive primigravidae, and 15 primigravidae with untreated preeclampsia. In pregnant subjects, FBF was reduced to nonpregnancy levels by infusion of norepinephrine (NE), which was then confounded with ANG II (2, 4, and 8 ng/min) and L-NMMA (200, 400, and 800 µg/min) each for 5 min. In separate studies, responses to NE (20, 50, and 100 ng/min) were determined in 8 nonpregnant women, with FBF elevated to pregnancy levels by concomitant infusion of glyceryl trinitrate, and 10 pregnant women. Vasoconstrictor responses to L-NMMA were increased in pregnant compared with nonpregnant subjects [mean ± SE summary measure (in arbitrary units): 60 ± 7 vs. 89 ± 8, respectively; P < 0.01], whereas responses to ANG II were blunted (125 ± 11 vs. 79 ± 7, respectively; P < 0.001). Compared with normotensive pregnant subjects, preeclamptic subjects had an enhanced response to ANG II (79 ± 7 vs. 103 ± 8, respectively; P < 0.05) but no difference in response to L-NMMA (89 ± 8 vs. 73 ± 10, respectively; P = 0.30). Responses to NE were similar in pregnant and nonpregnant subjects (110 ± 20 vs. 95 ± 33, respectively; P = 0.66). During the third trimester of pregnancy, forearm constrictor responses to L-NMMA are increased. The responses to NE are unchanged, whereas responses to ANG II are blunted. Increased NO activity contributes to the fall in peripheral resistance. In preeclampsia, forearm constrictor responses to ANG II but not L-NMMA are increased compared with those in normal pregnancy. Changes in vascular NO activity are unlikely to account for the increased vascular tone in this condition.

vascular resistance; N³-monomethyl-L-arginine

HUMAN PREGNANCY is associated with a profound reduction in vascular resistance, evident as early as the third week after conception (33). The primary circulatory change appears to be peripheral arterial vasodilatation with secondary stimulation of the renin-aldosterone axis and plasma volume expansion. In preeclampsia there is increased systemic vascular resistance (43), and aldosterone and plasma volume are reduced (17, 30). The mechanisms responsible for these hemodynamic changes are unknown. Nitric oxide (NO), a potent endothelial-derived vasodilator, has been shown to modulate peripheral vasodilator tone (41). Alterations in the L-arginine-NO pathway may modulate the changes in peripheral arterial tone in normal and preeclamptic pregnancy.

Indirect observations suggest that NO activity may be increased during normal human pregnancy; serum levels of nitrite and cGMP are increased (7). Further evidence that NO may mediate pregnancy-induced vasodilatation is provided by the findings of increased NO activity in the dorsal hand vein of puerperal women (13) and in the hand circulation during pregnancy (47).

Preeclampsia is associated with elevated levels of factor VIII-related antigen and fibronectin, which predate the clinical syndrome (5). These findings suggest that endothelial dysfunction is important in the pathogenesis and may lead to alterations in NO synthesis. In pregnant rats, prolonged blockade of NO synthesis produces a disorder similar to preeclampsia (hypertension, proteinuria, thrombocytopenia, and intrauterine growth retardation), and the features are reversed by L-arginine infusion (48). Isolated small arteries from women with preeclampsia demonstrate impaired endothelium-mediated vasodilatation (21, 27). However, studies of serum levels of NO metabolites (nitrites and nitrates) and cGMP in preeclampsia have been conflicting (7, 37, 38). No in vivo study has addressed the role of NO in the altered peripheral arterial tone in preeclampsia.

The primary aims of the present study were to determine whether increased NO activity contributes to the decreased vascular resistance in normal pregnancy and whether decreased NO activity contributes to the increased vascular resistance in preeclampsia. We also sought to determine whether vascular responsiveness to angiotensin and norepinephrine were altered during pregnancy.

METHODS

Subjects. Twenty healthy primiparous women, fifteen primiparous women with preeclampsia who had not received antihypertensive therapy, and twenty healthy nonpregnant women who were not using hormonal contraceptives were studied (Table 1). All subjects were nonsmokers and refrained from alcohol and caffeine for a minimum of 4 h before each study. Preeclamptic women had persistently elevated blood pressure readings of ≳140 mmHg systolic and 90 mmHg diastolic and proteinuria of ≳300 mg in 24 h or 2+ on dipstick. Written informed consent was obtained, and the studies were approved by the Newcastle Joint Ethics Committee.

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VASCULAR NO ACTIVITY IN PREECLAMPSIA.

Table 1. Subject details and constrictor responses to L-NMMA and angiotensin II

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Nonpregnant</th>
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<th>Pregant vs. Nonpregnant</th>
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<td>Gestational age, wk</td>
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<td>36 (31–41)</td>
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<td>Urine protein excretion, g/24 h</td>
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Values are expressed as means ± SE, or median (range) when distribution was not normal; for n = no. of women. MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; FVR, forearm vascular resistance. *P < 0.05, †P < 0.01, ‡P < 0.001, normotensive pregnant vs. nonpregnant and preeclamptic vs. normotensive pregnant women.

Study protocol. Studies were carried out in a temperature-controlled quiet laboratory (25°C) with the subjects in a slight left lateral tilt to avoid caval occlusion. Forearm blood flow (FBF) was measured simultaneously in both arms by mercury-in-Silastic strain-gauge plethysmography (46). The Silastic strain gauges were placed around the largest circumference of each forearm, ~3–5 cm below the medial epicondyle. Drugs or physiological saline were infused at 1 ml/min continuously into the brachial artery of the nondominant arm through a 27-SWG needle introduced under local anesthesia. At the start of each study, after the needle was inserted, basal blood flow measurements were taken for 30 min (during infusion of saline) to establish resting control values. For each blood flow measurement period, the wrist cuffs were inflated above systolic pressure (200 mmHg) to exclude the hand circulation. Exclusion of hand blood flow improves the accuracy and reproducibility of FBF measurements by venous occlusion plethysmography (24). These wrist cuffs were inflated for ~1 min before FBF measurements were taken to allow stabilization of flow. The upper arm congesting (venous occlusion) cuffs were then inflated above venous pressure (40 mmHg), leading to an increase in forearm volume due to arterial inflow. After ~10 s, the venous occlusion cuffs were deflated for 5 s to allow the tracing to return to baseline with venous emptying from the forearm. Repeated measurements were made, with each inflation of the upper arm congesting cuffs yielding a flow measurement. For each measurement period, five 15-s cycles of venous occlusion and deflation enabled five flow measurements to be obtained, the mean of which was derived. Blood pressure was measured in the control arm every 15 min using a semiautomated oscilometric device.

All drugs were dissolved in sterile physiological saline immediately before infusion. After resting control FBF measurements were obtained, each subject received three doses of human angiotensin II (ANG II; 2, 4, and 8 ng/min, each for 5 min). Saline was then infused until FBF returned to control values (median time 15 min; range 10–40 min). Subjects then received three doses of N⁵-monomethyl-L-arginine (L-NMMA; 200, 400, and 800 μg/min, each for 5 min) to produce a cumulative dose response. Blood flow was recorded during the last 2 min of each 5-min drug infusion period, when responses to L-NMMA and ANG II had stabilized.

To overcome the potential confounding effects of elevated flow on NO release and the differential dilutional effects of infused drugs between study groups, FBF in the pregnant and preeclamptic subjects was reduced to nonpregnancy levels by initial infusion of norepinephrine (median dose 10 ng/min, range 5–30 ng/min). The dose of norepinephrine required to achieve this was then confirmed with ANG II and L-NMMA as described above.

In a subsequent study the forearm constrictor responses to norepinephrine were determined in 8 nonpregnant and 10 normotensive pregnant subjects (Table 2). To overcome the potential confounding effects of differences in baseline FBF between groups, basal FBF was elevated in the nonpregnant subjects by glyceryl trinitrate (GTN; 10–25 ng/min), an endothelium-independent NO donor. After the baseline FBF was established, three doses of norepinephrine (20, 50, and 100 ng/min) were infused, each for 5 min.

Data capture and statistical analysis. Data were recorded directly onto a computer using a MacLab system with on-line slope analysis to determine FBF. The average of the five slopes for each measurement period was derived to determine FBF. FBF was expressed as milliliters per 100 milliliters of forearm per minute according to the method of Whitney (46). Forearm vascular resistance (FVR) was derived from mean arterial pressure (MAP) and baseline FBF. Differences in baseline heart rate, blood pressure, FBF, and FVR between groups were compared by Student’s t-test. Within-subject differences in FBF in the control and infused arms were assessed using two separate repeated-measures ANOVA. Further analysis was undertaken if ANOVA suggested a statistically significant change in FBF over time.

FBF responses were expressed as a percentage of FBF during baseline infusion of saline or norepinephrine. The overall response to each drug in each subject was assessed by summary measures (47): the maximal response and an overall response calculated as the summation of the percent-age constrictor responses for the three doses of the infused drug (arbitrary units). The rationale for the clinical and statistical application of summary measures for analysis of serial measurements has been discussed by Matthews et al. (25). Values are expressed as means ± SE and were compared using Student’s t-test or the Mann-Whitney U test as appropriate. P < 0.05 was considered statistically significant.

Instrumentation and drugs. Mercury strain gauges and plethysmographs were supplied by D. E. Hokansen (Bellevue, WA), and the twin-cuff inflators were obtained from Technomed Medical Services (Surrey, UK). The continuous syringe infusion pumps were obtained from Welmed (Bramley, UK). The 27-SWG needles were obtained from Cooper’s Needleworks.

Table 2. Subject details and constrictor responses to norepinephrine

<table>
<thead>
<tr>
<th>Characteristics</th>
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<th>Pregnant</th>
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<tbody>
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<td>MAP, mmHg</td>
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<td>SBP, mmHg</td>
<td>126 ± 3</td>
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<tr>
<td>DBP, mmHg</td>
<td>69 ± 2</td>
<td>68 ± 3</td>
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<tr>
<td>FVR, mmHg·ml⁻¹·min⁻¹·100 ml</td>
<td>38 ± 3</td>
<td>25 ± 3†</td>
</tr>
<tr>
<td>Forearm volume, ml</td>
<td>708 ± 31</td>
<td>733 ± 20</td>
</tr>
<tr>
<td>Forearm length, cm</td>
<td>26 ± 0.4</td>
<td>26 ± 0.4</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>37 (28–38)</td>
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</table>

Values are expressed as means ± SE, or median (range) when distribution was not normal; for n = no. of women. *P < 0.05, †P < 0.01, pregnant vs. nonpregnant women.
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RESULTS

Constrictor responses to L-NMMA and ANG II. Subject details are shown in Table 1. Pregnant subjects had reduced FVR but similar blood pressure compared with nonpregnant subjects. Blood pressure and FVR were higher in preeclamptic compared with pregnant subjects. The weights of preeclamptic subjects but not forearm volume or length were greater than those of pregnant subjects.

FBF did not vary significantly in the noninfused arm in any of the groups during the study. Basal FBF did not differ between pregnant (3.6 ± 0.2 ml·100 ml⁻¹·min⁻¹) and nonpregnant subjects (4.2 ± 0.5 ml·100 ml⁻¹·min⁻¹) but was lower in nonpregnant subjects (2.8 ± 0.3 ml·100 ml⁻¹·min⁻¹, P < 0.05). Norepinephrine significantly lowered FBF in pregnant (2.9 ± 0.2 ml·100 ml⁻¹·min⁻¹, P < 0.05) and preeclamptic subjects (3.5 ± 0.4 ml·100 ml⁻¹·min⁻¹, P < 0.05) to levels comparable to those in nonpregnant subjects. The mean changes in FBF in the three groups are shown in Fig. 1. ANG II and L-NMMA produced dose-dependent falls in FBF in all subjects. The individual overall summary responses to ANG II and L-NMMA are shown in Fig 2. Whereas the constrictor response to ANG II was less in pregnant than in nonpregnant subjects at all dose levels (maximal response 35 ± 2 vs. 49 ± 4%, P < 0.01; overall summary response 79 ± 7 vs. 125 ± 11, P < 0.001), the response to L-NMMA was greater in pregnant than in nonpregnant subjects (maximal response 38 ± 3 vs. 24 ± 3%, P < 0.05; overall summary response 89 ± 8 vs. 60 ± 7, P < 0.01). Compared with pregnant subjects, preeclamptic subjects had an enhanced constrictor response to ANG II (maximal response 34 ± 2 vs. 41 ± 4%, P < 0.15; overall summary response 79 ± 7 vs. 103 ± 8, P < 0.05). There was no difference in constrictor response to L-NMMA between pregnant and preeclamptic subjects (maximum re-
tion between L-NMMA summary responses and basal summary response (maximal response were similar in pregnant and nonpregnant subjects infused, the constrictor responses to norepinephrine were similar in pregnant and nonpregnant subjects (maximal response vs. 40% P = 0.7; overall summary response vs. 95% P = 0.66).

DISCUSSION

This is the first in vivo study of forearm vascular NO activity in normotensive and preeclamptic women. It provides evidence that forearm vascular responses to NO synthase inhibition are enhanced in pregnancy. Furthermore, we have found no evidence to suggest that peripheral vascular NO activity is altered in preeclampsia.

Our findings do not support a generalized refractoriness to vasopressors during pregnancy. The blunted constrictor response to ANG II but not to norepinephrine is consistent with previous human in vitro studies using isolated arteries and in vivo studies of systemic pressor responses (14, 21). They also confirm the observations of Benjamin et al. (6), who infused ANG II into the brachial artery earlier in pregnancy. However, in contrast to the present findings, Williams et al. (47) reported a blunted constrictor response to norepinephrine in the hand circulation during late pregnancy compared with nonpregnancy and early pregnancy. Although this difference may reflect the different vascular bed studied, it is more likely to reflect differences in study design; Williams et al. (47) made no attempt to control for the higher baseline hand blood flow during late pregnancy. Thus the reduced constrictor response to norepinephrine in this group may reflect the lower concentration of drug reaching the resistance vessels. In contrast to ANG II and norepinephrine responses, those to NO synthase inhibition were increased in pregnant women. Because there is an enhanced constrictor response to L-NMMA in situations of high basal NO activity, our results suggest that basal NO activity is increased in late pregnancy. These findings are consistent with those of Williams et al. (47), who reported increased constriction to NO synthase inhibition with L-NMMA in the hand circulation of women during early (9–15 wk) and late (36–41 wk) pregnancy.

Altered vascular smooth muscle sensitivity to NO is unlikely to account for the increased vascular NO activity during pregnancy; responses to sodium nitroprusside (an NO donor) are similar in resistance vessel strips from pregnant and nonpregnant women (26). A more likely explanation for our findings is an increased synthesis of NO by the vascular endothelium (45). The mechanism of increased NO synthesis is uncertain, but estrogens, blood flow, and fluid shear stress may contribute. Increased expression of calcium-dependent NO synthase and increased amounts of mRNA endothelial and neuronal NO synthase isozymes (44, 45) have been reported in guinea pigs treated with estradiol. Upregulation of NO synthase in cultured endothelial cells is seen after 8 h of incubation with estradiol (19). These observations suggest that genomic mechanisms account for estrogen-mediated increases in NO activity.

Blood flow is a major regulator of endothelial NO production (34), and flow-induced dilatation has been shown in both animal (in vitro) and human (in vivo) models to be mediated, at least in part, by NO (20). Endothelial NO synthase can also be elevated by fluid shear stress independent of flow-induced NO production or protein kinase C activation (31). The NO response to flow involves an initial rapid, transient, and calcium/calmodulin-dependent phase and a more sustained calcium/calmodulin-independent phase (22). Although both phases appear to be mediated by endothelial NO synthase, the signal transduction pathways are unclear. Cockell et al. (11) have shown that NO-mediated responses to flow are exaggerated in arteries from fat biopsies in healthy pregnant women and that incubation of vessel strips with estradiol enhances flow-induced vasodilatation in prepubertal female rats (10). Thus estradiol may contribute to flow-related NO synthesis in pregnancy. However, the relative importance of elevated blood flow to enhanced NO activity remains to be determined. The fact that Williams et al. (47) found enhanced constrictor responses to L-NMMA in early pregnancy when hand blood flow was not increased suggests that flow-independent mechanisms may be more important.

It has been postulated that endothelial dysfunction (5) and loss of endothelium-mediated vasodilatation (11) may account for the increased vascular resistance in women with preeclampsia. Our observations do not support a major role for suppressed vascular NO synthesis in this condition. Although administration of high doses of NO synthase inhibitors produces a syndrome of hypertension and proteinuria in pregnant rats (48), these findings may be of limited relevance to preeclampsia in humans, particularly because these experiments employed very high doses of NO synthase inhibitors. Furthermore, similar features are observed when an inhibitor of NO synthesis is administered to nonpregnant animals, suggesting that the link of NO synthesis inhibition to a syndrome similar to preeclampsia is questionable.

In vitro human studies of the L-arginine-NO system in preeclampsia have shown conflicting results. Serum cGMP levels are increased (7, 35), but this may reflect increased plasma atrial natriuretic peptide (ANP) levels in preeclampsia. Indeed, Schneider et al. (35) reported a positive correlation between plasma ANP and cGMP levels in preeclampsia. Serum levels of nitrites
and nitrates in preeclampsia are conflicting (15, 37, 38) and may not accurately reflect NO activity in the arterial vasculature.

Dietary sources of nitrates and nitrates were not controlled for in these studies, and one study included women who had received magnesium sulfate, which decreases circulating ionized calcium levels and may downregulate calcium-dependent constitutive NO synthase (37). Cultured endothelial cells exposed to serum from preeclamptic women have increased (3) or normal NO synthesis (7, 38). The increased NO production rates reported by Baker et al. (3) were no longer evident when cells were cultured in the presence of shear stress (4). Taken together, these findings suggest that the L-arginine-NO pathway is not attenuated in the peripheral vasculature in preeclampsia.

Wire myographic studies of isolated subcutaneous arteries from women with preeclampsia have shown impaired relaxation to ACh and bradykinin compared with arteries from normotensive pregnant controls (21, 26, 27). In contrast, Pascoal et al. (29) reported impairment of ACh- but not bradykinin-mediated relaxation in isolated omental arteries from women with preeclampsia. However, dilator responses to these agonists are only partly NO dependent and are therefore difficult to interpret. Tonic vasodilatation is more likely to be regulated by basal NO release, which was not investigated in these studies. Furthermore arteries in vitro are not exposed to physiological shear stress, which alters the effects of plasma on endothelial production of NO (4) and is the principle stimulus to endothelial NO synthesis (18).

Despite our observations in forearm vasculature, it is possible that the L-arginine-NO pathway may be selectively attenuated in other tissues. Studies of placental NO synthase activity are conflicting, with decreased (28) or unchanged (12) placental NO synthase activity being reported. Total nitrates have even been reported to be increased in the fetoplacental circulation in preeclampsia, suggesting that increased NO production may be a compensatory response to improve blood flow or may play a role in limiting platelet adhesion and aggregation.

Women with preeclampsia showed an enhanced constrictor response to ANG II, consistent with studies of systemic pressor responses (14). The mechanisms of this enhanced response are unclear; plasma ANG II levels are reduced in preeclampsia (16), and this could lead to upregulation of vascular smooth muscle angiotensin receptors. The enhanced platelet ANG II binding reported in women with preeclampsia is consistent with this hypothesis (2). Other factors that have been implicated in the increased systemic vascular resistance in preeclampsia include increased plasma levels of endothelin (39), alterations in the ratio of thromboxane A2 to prostacyclin (9), and sympathetic overactivity (36). Blood flow is likely to be an important confounding influence on studies of vascular NO activity during pregnancy; acute elevation of forearm flow by 35% has been shown to increase the constrictor response to NO synthase inhibition by 40% (8). In an attempt to overcome the potential confounding effect of increased flow on the response to NO synthase inhibition together with the differential dilutional effects of the infused drugs, we reduced FBF in pregnant women to nonpregnant values using norepinephrine. However, acutely reducing blood flow may not correct for any chronic effect of elevated flow on NO synthase activity. We chose norepinephrine because it induces endothelium-independent vasoconstriction, predominantly via activation of α1-adrenoceptors (40). The drug has been extensively employed as an NO-independent vasoconstrictor in this vascular bed (8, 47). However, there is evidence that endothelial α2-adrenoceptor stimulation induces endothelium-dependent NO-mediated relaxation (42). The degree to which endothelial cells in the human forearm express α2-adrenoceptors and whether stimulation leads to NO release are unclear. One study in the human forearm suggested that norepinephrine had no apparent effect on endothelial-dependent vasoconstriction (32). Furthermore, we have subsequently shown that constrictor responses to L-NMMA in pregnant women without norepinephrine-induced flow reduction (mean overall summary measure 81 ± 11; Ref. 1) are similar to those reported in the present study. Thus, although we cannot exclude a small α2-adrenoceptor-mediated stimulation of NO by norepinephrine, this mechanism is unlikely to principally account for the differences observed between pregnant and nonpregnant subjects.

In conclusion, we have shown that NO activity is increased in the peripheral vasculature during pregnancy. This suggests that NO contributes to the decrease in systemic vascular resistance characteristic of pregnancy. However, we have found no evidence in the forearm vasculature to suggest that reduced NO activity contributes to increased vascular resistance in preeclampsia. Whereas NO donors, currently being explored as potential therapies in preeclampsia (23), may alleviate some features of the disorder, they may not correct the underlying pathophysiological deficit. Furthermore, L-arginine supplementation in women with preeclampsia in the absence of attenuated NO activity is unlikely to be of value.

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