

## PREECLAMPSIA — A STATE OF SYMPATHETIC OVERACTIVITY

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**ABSTRACT**

**Background** Preeclampsia is characterized by a marked increase in peripheral vascular resistance leading to an increase in blood pressure, but the triggering mechanisms are unclear.

**Methods** To determine whether augmented sympathetic vasoconstrictor activity may be an important mechanism in mediating the increase in vasomotor tone, we measured postganglionic sympathetic-nerve activity in the blood vessels of skeletal muscle by means of intraneural microelectrodes in nine women with preeclampsia, eight normotensive pregnant women, six normotensive nonpregnant women, and seven nonpregnant women with hypertension, both at rest and during noninvasive cardiovascular-reflex testing (with the Valsalva maneuver and the cold pressor test).

**Results** The mean ( $\pm$ SE) rate of sympathetic-nerve activity in the normotensive pregnant women ( $10 \pm 1$  bursts per minute) was not significantly different from that in normotensive nonpregnant women ( $12 \pm 2$  bursts per minute) or hypertensive nonpregnant women ( $15 \pm 3$  bursts per minute). In contrast, the rate of sympathetic-nerve activity in the patients with preeclampsia ( $33 \pm 3$  bursts per minute) was more than three times as high as that in the normotensive pregnant women ( $P < 0.05$ ) and more than twice as high as in the group of nonpregnant women with hypertension ( $P < 0.05$ ). Hemodynamic and sympathetic-nerve responses to both reflex tests did not differ significantly among the four groups. Six patients with preeclampsia were studied again after delivery; mean sympathetic-nerve activity at that time had decreased significantly from the value during pregnancy (from  $36 \pm 4$  to  $13 \pm 2$  bursts per minute,  $P < 0.01$ ), as had mean arterial pressure (from  $118 \pm 3$  to  $96 \pm 1$  mm Hg,  $P < 0.01$ ).

**Conclusions** Preeclampsia is a state of sympathetic overactivity, which reverts to normal after delivery. Our data indicate that the increases in peripheral vascular resistance and blood pressure that characterize this disorder are mediated, at least in part, by a substantial increase in sympathetic vasoconstrictor activity. (N Engl J Med 1996;335:1480-5.)

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**P**REECLAMPSIA is a hypertensive disorder of late pregnancy that resolves shortly after delivery. It occurs in up to 10 percent of all pregnancies and is a major cause of maternal and fetal morbidity and mortality.<sup>1-3</sup> Although the pathophysiologic mechanisms that underlie this uniquely reversible form of human hypertension still remain to be elucidated, it is now clear that pre-

eclampsia is characterized by a marked increase in peripheral vascular resistance, which, in turn, causes the increase in blood pressure.<sup>4,5</sup> Studies in animals have suggested that endothelial dysfunction with an imbalance of vasodilating and vasoconstricting substances (nitric oxide deficiency) may account for this disorder.<sup>6,7</sup> Recent clinical studies in humans, however, have conflicting results with regard to the role of nitric oxide in preeclampsia.<sup>8-11</sup>

Since vascular tone is largely determined by the activity of the sympathetic nervous system, we decided to examine whether an increase in sympathetic vasoconstrictor activity may be an important mechanism in mediating the increase in peripheral vascular resistance in preeclampsia. We therefore measured postganglionic action potentials in sympathetic-nerve fibers innervating blood vessels in the skeletal muscle in patients with preeclampsia. Measurements in the hypertensive state were compared with those made after delivery, when blood pressure was again normal. Sympathetic-nerve activity was also measured in normotensive pregnant women and in nonpregnant women with and without hypertension.

**METHODS****Subjects**

We studied 30 white women: 9 women with preeclampsia; 8 normotensive pregnant women matched with the women who had preeclampsia for age, week of gestation, and body weight; 6 normotensive nonpregnant women of similar age; and 7 nonpregnant women of similar age who had hypertension (Table 1). Preeclampsia was defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy. These criteria include no history of hypertension, cardiovascular, or renal disease before pregnancy and blood-pressure values exceeding 140/90 mm Hg after the 20th week of gestation, confirmed by two consecutive readings at least six hours apart, with blood pressure reverting to normal within 2 months after delivery.<sup>1</sup>

Eight of the nine women with preeclampsia had proteinuria of  $>500$  mg per day. One woman who did not have substantial proteinuria had other signs of preeclampsia, such as thrombocytopenia (platelet count, 98,000 per cubic millimeter; normal,  $>150,000$  per cubic millimeter) and mild elevation of aminotransferase values (aspartate aminotransferase, 28 U per liter; normal,  $<15$  U per liter; alanine aminotransferase, 25 U per liter; normal,  $<17$  U per liter). Further characteristics of preeclampsia found in these patients were hypoalbuminemia (serum albumin,  $3.0 \pm 0.2$  g per deciliter; normal range, 3.5 to 5.0 g per deciliter),

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TABLE 1. CHARACTERISTICS OF THE FOUR GROUPS OF SUBJECTS.\*

CHARACTERISTIC	WOMEN WITH PREECLAMPSIA (N=9)	NORMOTENSIVE PREGNANT WOMEN (N=8)	NORMOTENSIVE NONPREGNANT WOMEN (N=6)	HYPERTENSIVE NONPREGNANT WOMEN (N=7)
Age (yr)	26±1	26±1	25±1	27±2
Wk of gestation	33±1	32±1	—	—
Primigravida (no. of women)	9	6	—	—
Weight (kg)	76±6	75±5	66±4†	67±6†
Height (m)	1.66±0.03	1.65±0.03	1.67±0.04	1.68±0.04
Body-mass index‡	27.5±0.2	27.6±0.2	23.7±0.1†	23.9±0.2†

\*Plus-minus values are means ±SE.

†P<0.05 for the comparisons with the women with preeclampsia and the normotensive pregnant women.

‡The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.

hyperuricemia (serum uric acid, 6.2±0.4 mg per deciliter [370±20 μmol per liter]; normal range, 2.4 to 5.7 mg per deciliter [140 to 340 μmol per liter]), and mild relative hemoconcentration (serum hematocrit, 42±1 percent; normal value in the third trimester, <38 percent).

The women with preeclampsia were recruited from the perinatal ward of the Nuremberg community hospital, where they were hospitalized because of an increase in blood pressure in the third trimester. The patients with preeclampsia and the control subjects were following no special diet, and there was no restriction of salt intake. All patients were examined within one to two days after hospitalization.

Five of the nine patients with preeclampsia received the vasodilator drug dihydralazine (Nepresol, Ciba; 25 mg taken orally) as antihypertensive medication on admission. No other antihypertensive drugs were given, and none of the patients were receiving antihypertensive medication before their hospitalization. Three of these five women received one tablet shortly after hospitalization and were studied with microneurography within the next 12 to 24 hours. Two of the five patients were studied 48 hours after hospitalization. These patients had received a total dose of three tablets of dihydralazine within the first 36 hours after admission. Thus, the interval between the intake of the last tablet of dihydralazine and the microneurographic study was at least 12 hours for each patient, or three times the elimination half-life of dihydralazine. The remaining four patients with preeclampsia received no antihypertensive medication before the study.

The normotensive pregnant controls were also hospitalized because of obstetrical complications at the time of the study but were otherwise healthy; they remained normotensive throughout their pregnancies. None of these women were taking medications other than iron or vitamins. The nonpregnant normotensive controls were members of the medical and laboratory staff. The nonpregnant control women with hypertension were recruited from among patients at our hypertension clinic. These patients were selected because they were taking antihypertensive drugs similar to those received by the women with preeclampsia (dihydralazine or other vasodilators such as dihydropyridine calcium antagonists), which were discontinued 12 to 24 hours before the study. The protocol was approved by the Institutional Review Board on Human Investigation of the University of Erlangen-Nürnberg, and all the women provided written informed consent.

**General Procedures**

All the women were studied between 9 a.m. and noon without sedation in the postabsorptive state (i.e., at least 90 minutes after

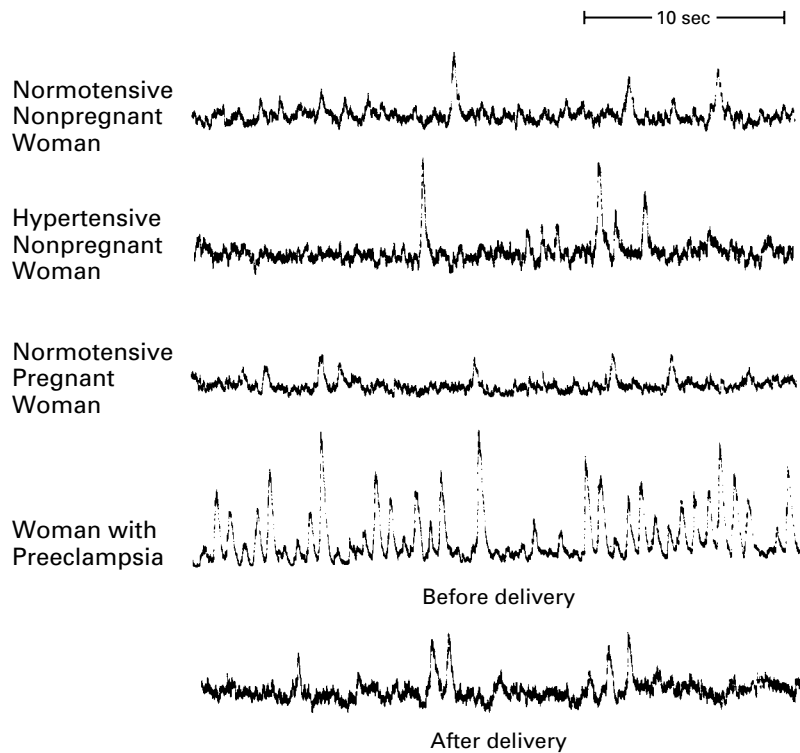
the ingestion of a light breakfast). The studies were performed with all pregnant subjects lying in a 30-degree left lateral position. A direct-writing multichannel physiologic recorder (Gould Instruments) was used to make simultaneous recordings of blood pressure (measured noninvasively beat to beat by a photoplethysmographic finger device; Finapres, Ohmeda), heart rate (measured by electrocardiography), respiratory excursions (measured with a pneumograph), and efferent sympathetic-nerve activity to the vasculature of the leg muscles. Respiratory excursions were monitored to detect the inadvertent performance of a Valsalva maneuver or prolonged expiration, since these respiratory maneuvers stimulate sympathetic outflow.<sup>12</sup>

**Recordings of Sympathetic-Nerve Activity**

Multunit recordings of postganglionic sympathetic-nerve activity were obtained with unipolar tungsten microelectrodes inserted selectively into muscle-nerve fascicles of the peroneal nerve posterior to the fibular head by the microneurographic technique of Vallbo et al.<sup>13</sup> The electrodes were connected to a preamplifier, and the nerve signal was fed through a bandpass filter and routed through an amplitude discriminator to a storage oscilloscope and loudspeaker.

For recording and analysis, the filtered neurogram was fed through a resistance-capacitance integrating network to obtain a display of the mean voltage of the neural activity. A recording of sympathetic activity was considered acceptable when the neurogram revealed spontaneous, pulse-synchronous bursts of neural activity, with the largest bursts showing a minimal signal-to-noise ratio of 3:1. In each study, we also confirmed that we were recording the sympathetic outflow to skeletal muscle rather than sympathetic discharge to skin by demonstrating that the neural activity did not change in response to arousal stimuli or a pinch of the skin but showed a characteristically biphasic response to the Valsalva maneuver.<sup>12</sup>

For analysis, sympathetic bursts were identified by inspection of the filtered and mean-voltage neurograms. The rate of sympathetic-nerve discharge was expressed as the number of bursts per minute. Sympathetic activity was also corrected for heart rate and expressed as bursts per 100 heartbeats.<sup>14</sup> All nerve recordings were analyzed by two investigators who were unaware of the group assignment of the subjects. The data on sympathetic-nerve activity given in the text and figures of this article represent the mean for the two observers. Results and conclusions did not differ significantly between observers. As in earlier studies,<sup>15</sup> the intraobserver variation in identifying bursts was 5 percent, and the interobserver variation was less than 10 percent.



**Figure 1.** Representative Recordings of Sympathetic-Nerve Activity in a Normotensive Nonpregnant Woman, a Hypertensive Nonpregnant Woman, a Normotensive Pregnant Woman, and a Woman with Preeclampsia (before and after Delivery).

The rate of sympathetic-nerve discharge was similar in the two nonpregnant women and the normotensive pregnant woman, but it was much higher in the patient with preeclampsia. After delivery, blood pressure and sympathetic activity returned to normal in this patient.

### Study Protocol

To ensure that the base-line values were stable, all subjects rested quietly for 30 minutes after the nerve electrode had been inserted and the other monitoring devices had been applied. Blood pressure, heart rate, respiratory excursions, and sympathetic-nerve activity at rest were then recorded continuously for at least 20 minutes. The reported values for these variables represent the means for this period. After registration of the base-line data, two cardiovascular-reflex tests were performed to assess the autonomic neural control of the circulation.

We compared the responses of the heart rate and muscle sympathetic-nerve activity during performance of the Valsalva maneuver, which is a standard noninvasive test to assess baroreflex function.<sup>16</sup> This maneuver was performed by instructing subjects to exhale into a manometer with an expiratory pressure of 40 mm Hg for 15 seconds. In each subject we determined the Valsalva ratio, which was calculated as the ratio of the longest R-R interval shortly after exhalation to the shortest R-R interval during the exhalation, and the increase in sympathetic-nerve activity during the maneuver.

A cold pressor test was used as a non-baroreflex-mediated sympathoexcitatory stimulus.<sup>17</sup> In the test, one of the subject's hands was immersed up to the wrist in ice water for two minutes. Control and recovery periods for the cold pressor test were also two minutes in duration. The average response during each period of control, intervention, and recovery was determined.

In six of the nine patients with preeclampsia, measurements

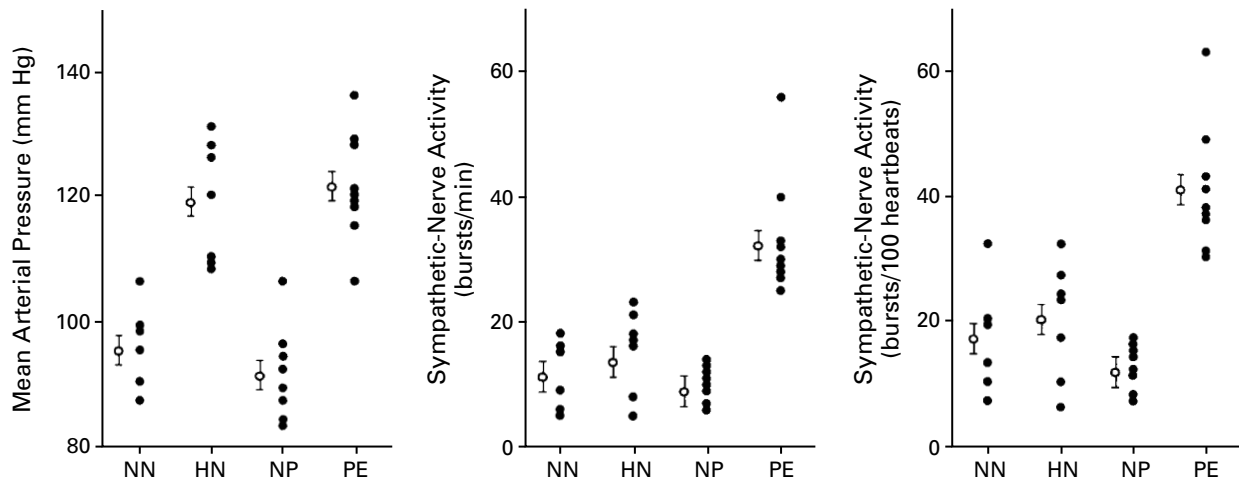
were repeated one to three months after delivery, when the blood pressure was normal again, to determine whether the changes in blood pressure were accompanied by similar changes in sympathetic activity.

### Statistical Analysis

The differences in the mean base-line values as well as the responses to the Valsalva maneuver and the cold pressor test among the four groups were compared by analysis of variance with Fisher's test for the least significant difference in comparisons between pairs of groups. Paired t-tests (two-tailed) were used for the comparisons of sympathetic activity and mean arterial blood pressure before and after delivery within the group with preeclampsia. Statistical significance was considered indicated by a P value of less than 0.05. Values are presented as means  $\pm$  SE.

### RESULTS

The characteristics of the four study groups are shown in Table 1, and representative recordings of sympathetic-nerve activity in each group are shown in Figure 1. The rate of sympathetic discharge in the normotensive pregnant women did not differ significantly from that in the nonpregnant normotensive women or the nonpregnant women with hyperten-



**Figure 2.** Mean Arterial Pressure and Sympathetic-Nerve Activity in Six Normotensive Nonpregnant Women (NN), Seven Hypertensive Nonpregnant Women (HN), Eight Normotensive Pregnant Women (NP), and Nine Women with Preeclampsia (PE). The solid circles are individual values, and the open circles and bars are the group means  $\pm$ SE. Mean arterial pressure was similarly elevated in the patients with preeclampsia and the nonpregnant women with hypertension, as compared with the two normotensive groups ( $P < 0.05$  for each comparison). Sympathetic-nerve activity, however, was markedly increased in the patients with preeclampsia but not in the nonpregnant women with hypertension ( $P < 0.05$  for the comparison of the women with preeclampsia with all other groups).

sion ( $10 \pm 1$  vs.  $12 \pm 2$  and  $15 \pm 3$  bursts per minute, respectively;  $P$  not significant for the comparisons among groups) (Fig. 1 and 2). In contrast, with a mean value of  $33 \pm 3$  bursts per minute, sympathetic activity was more than three times as high in the patients with preeclampsia as in the normotensive pregnant women ( $P < 0.05$ ), and more than twice as high as in the group of age-matched nonpregnant women with hypertension ( $P < 0.05$ ) (Fig. 2). Because of the matching procedure, the group with preeclampsia did not differ significantly from the group of normotensive pregnant women with regard to age, week of gestation, or body-mass index (Table 1).

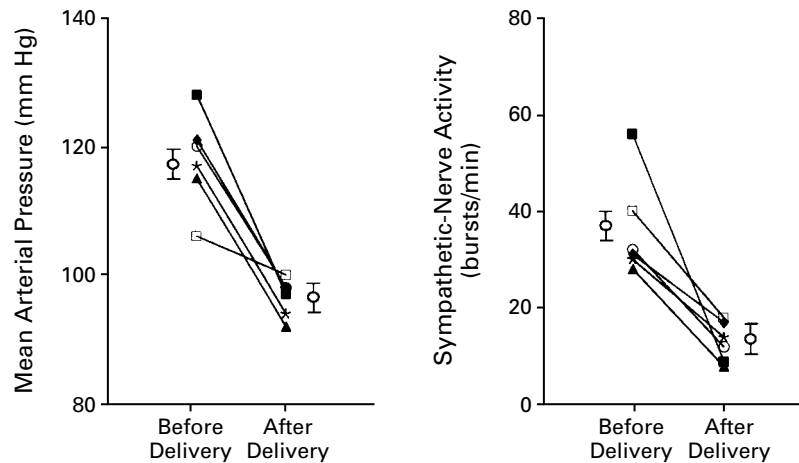
The heart rate was similarly elevated in both groups of pregnant women ( $82 \pm 2$  bpm in the patients with preeclampsia and  $82 \pm 3$  in the normotensive pregnant women), as compared with the normotensive nonpregnant control group ( $70 \pm 4$  beats per minute,  $P < 0.05$  for each comparison), and it tended to be higher in the two groups of pregnant women than in the nonpregnant women with hypertension ( $76 \pm 4$  beats per minute,  $P$  not significant). Therefore, the marked increase in sympathetic-nerve firing in women with preeclampsia, as compared with normotensive pregnant women, cannot be explained by differences in the heart rate. This is also reflected in the fact that the mean value for sympathetic-nerve activity corrected for heart rate was much higher in the group with preeclampsia ( $41 \pm 3$  bursts per 100 heartbeats) than in the normotensive pregnant group ( $13 \pm 1$  bursts per 100 heartbeats,  $P < 0.05$ ). The

values for the normotensive and the hypertensive nonpregnant women ( $17 \pm 4$  and  $20 \pm 4$  bursts per 100 heartbeats, respectively) were also significantly lower than that for the patients with preeclampsia ( $P < 0.05$  for each comparison) (Fig. 2).

As was expected, mean arterial pressure was significantly higher in the patients with preeclampsia ( $121 \pm 3$  mm Hg) than in the normotensive pregnant women ( $92 \pm 3$  mm Hg,  $P < 0.05$ ) or the normotensive nonpregnant women ( $96 \pm 3$  mm Hg,  $P < 0.05$ ). The nonpregnant women with hypertension had mean arterial pressures that were very similar to those of the women with preeclampsia ( $119 \pm 5$  mm Hg,  $P$  not significant) (Fig. 2).

The responses of the heart rate and muscle sympathetic-nerve activity to the Valsalva maneuver did not differ significantly among the four groups. This was reflected in similar values for the Valsalva ratio (women with preeclampsia,  $1.5 \pm 0.2$ ; normotensive pregnant women,  $1.6 \pm 0.1$ ; normotensive nonpregnant women,  $1.6 \pm 0.1$ ; nonpregnant women with hypertension,  $1.5 \pm 0.1$ ;  $P$  not significant for the comparisons between groups), and similar increases in sympathetic-nerve activity during the Valsalva maneuver in the four groups ( $9 \pm 2$ ,  $11 \pm 2$ ,  $12 \pm 3$ , and  $10 \pm 2$  bursts per minute, respectively;  $P$  not significant).

Similarly, increases in mean arterial pressure, heart rate, and sympathetic-nerve activity during the cold pressor test did not differ significantly among the patients with preeclampsia ( $13 \pm 1$  mm Hg,  $4 \pm 2$  beats per minute, and  $9 \pm 3$  bursts per minute, respectively), the normotensive pregnant women ( $15 \pm 3$



**Figure 3.** Mean Arterial Pressure and Sympathetic-Nerve Activity in Six Women with Preeclampsia, Measured before and after Delivery.

The patients had nearly parallel decreases in blood pressure and sympathetic-nerve activity after delivery. The open circles and bars are the mean values  $\pm$ SE. The mean values before and after delivery differed significantly ( $P < 0.01$ ).

mm Hg,  $5 \pm 2$  beats per minute, and  $12 \pm 4$  bursts per minute), the normotensive nonpregnant women ( $13 \pm 3$  mm Hg,  $3 \pm 1$  beats per minute, and  $13 \pm 4$  bursts per minute), and the nonpregnant women with hypertension ( $16 \pm 4$  mm Hg,  $5 \pm 2$  beats per minute, and  $10 \pm 3$  bursts per minute;  $P$  not significant for all comparisons among the four groups).

Figure 3 compares the data on mean arterial pressure and sympathetic-nerve activity before and after delivery (range, 1 to 3 months) in six patients with preeclampsia. Group values for mean arterial pressure normalized; they fell from  $118 \pm 3$  mm Hg to  $96 \pm 1$  mm Hg ( $P < 0.01$ ) after delivery in these patients. The decrease in blood pressure was accompanied by a significant decrease in the mean sympathetic discharge, from  $36 \pm 4$  to  $13 \pm 2$  bursts per minute ( $P < 0.01$ ) and from  $43 \pm 5$  to  $17 \pm 2$  bursts per 100 heartbeats ( $P < 0.01$ ). The responses in each patient show almost parallel decreases in mean arterial pressure and sympathetic-nerve activity. Figure 1 shows this decrease in sympathetic activity after delivery in a patient with preeclampsia.

## DISCUSSION

We found that sympathetic vasoconstrictor discharge to skeletal muscle was markedly elevated in patients with preeclampsia but was normal in normotensive pregnant subjects. Shortly after delivery, furthermore, both blood pressure and sympathetic activity normalized in the women with preeclampsia. These findings suggest that the increase in peripheral vascular resistance seen in preeclampsia is mediated at least partly by a substantial increase in sympathetic vasoconstrictor activity.

Previous attempts to study the effects of the sympathetic nervous system on the development of hypertension in pregnancy focused mainly on plasma and urinary catecholamine concentrations, which ranged from increased to decreased.<sup>18-20</sup> These conflicting results may be explained by the now well-accepted fact that plasma and urinary catecholamine levels are insensitive measures of sympathetic activity that are influenced by many factors, such as efferent neural activity, synaptic transmitter release, reuptake mechanisms, and regional blood flow.<sup>21</sup> Pregnancy may lead to changes in catecholamine metabolism and clearance. In contrast, the microneurographic technique for obtaining direct intraneural recordings of postganglionic sympathetic-nerve activity allows a precise, quantitative, and reproducible assessment of sympathetic neural vasoconstrictor activity.

Our results obtained with this method indicate that preeclampsia is a state of sympathetic overactivity that reverts to normal after delivery. The finding of almost parallel decreases in sympathetic activity and blood pressure after delivery is highly suggestive of a neurogenic component in preeclampsia. This increase in sympathetic activity was a robust finding and was unrelated to the women's age, week of gestation, or body-mass index or to changes in heart rate. Furthermore, this sympathetic overactivity seems to be specific to the disease and is probably not a secondary finding caused by high blood pressure, since age-matched nonpregnant subjects with hypertension did not have significant increases in sympathetic activity.

At least three potential mechanisms may account for this sympathetic activation. The increase in sympathetic vasoconstrictor activity could be due either

to a decrease in baroreceptor-mediated inhibitory restraint on central sympathetic outflow or to central neural mechanisms. Alternatively, it is possible that humoral or paracrine factors could act in the central nervous system to enhance sympathetic-nerve activity. The literature provides some limited evidence of these suggested mechanisms. Ekholm and colleagues,<sup>22</sup> studying the changes in blood pressure and heart rate during noninvasive cardiovascular-reflex testing, found some changes in autonomic baroreflex-mediated circulatory control in patients with preeclampsia; however, other investigators<sup>23,24</sup> reported conflicting results.

In this study, we assessed baroreflex-mediated control of the heart rate and sympathetic-nerve activity by performing a Valsalva maneuver; we also examined the hemodynamic and sympathetic-nerve responses to a cold pressor test, a non-baroreflex-mediated sympathoexcitatory stimulus. Since responses to these cardiovascular-reflex tests were not significantly different in the group with preeclampsia and the control groups, the marked increase in basal sympathetic outflow to muscle in patients with preeclampsia does not seem to be due to an impairment of baroreflex-mediated sympathetic-nerve control or to a nonspecific change in general reflex responsiveness. Passloer<sup>25</sup> suggested that a defect in central conflict-processing systems may mediate an increase in catecholamine levels, which not only provokes somatic and affective symptoms of anxiety and hostility but also leads to an increase in peripheral vascular resistance and blood pressure.

The precise mechanisms underlying the increased sympathetic-nerve activity cannot be determined from our study. Another limitation of the study is the fact that sympathetic outflow to skeletal muscle may not reflect sympathetic activity in other organs, including the heart and kidneys.

Indirect evidence of a sympathetically mediated increase in blood pressure in patients with preeclampsia is provided by the well-known clinical effectiveness of sympatholytic therapy. Thus, methyl dopa, which acts by reducing central sympathetic outflow, is the treatment of choice for long-term control of blood pressure in patients with this disorder.<sup>5</sup>

In conclusion, the fundamental hemodynamic characteristic of preeclampsia is a marked increase in peripheral vascular resistance. Our studies suggest that augmented sympathetic vasoconstrictor activity is one important mechanism producing this increase in vascular resistance.

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