Sympathetic Neural Mechanisms in Normal and Hypertensive Pregnancy in Humans

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Background—Direct recordings from peripheral sympathetic nerves have shown an increased sympathetic drive in pregnancy-induced hypertension (PIH) and preeclampsia (PE). It is unknown whether sympathetic drive is altered in normal pregnancy, when arterial blood pressure can be normal or relatively low. The aim of this study was to measure and compare peripheral sympathetic discharge, its vasoconstrictor effect and its baroreceptor control, during pregnancy and postpartum in women with normal pregnancy (NP) and PIH and in normotensive nonpregnant (NN) women.

Methods and Results—Twenty-one women with NP, 18 women with PIH, and 21 NN women had muscle sympathetic nerve activity assessed from multiunit discharges (MSNA) and from single units with defined vasoconstrictor properties (s-MSNA). The s-MSNA in NP (38±6.6 impulses/100 beats) was greater (P<0.05) than in NN women (19±1.8 impulses/100 beats) despite similar age and body weight but less than in PIH women (P<0.001) (146±23.5 impulses/100 beats). MSNA followed a similar trend. Cardiac baroreceptor reflex sensitivity (BRS) was impaired in NP and PIH women relative to NN. After delivery, sympathetic activity decreased to values similar to those obtained in NN, and there was an increase in BRS. In women with NP, the decrease in sympathetic output occurred despite an insignificant change in blood pressure.

Conclusions—Central sympathetic output was increased in women with normal pregnancy and was even greater in the hypertensive pregnant group. The findings suggest that the moderate sympathetic hyperactivity during the latter months of normal pregnancy may help to return the arterial pressure to nonpregnant levels, although when the increase in activity is excessive, hypertension may ensue. (Circulation. 2001;104:2200-2204.)

Key Words: nervous system, autonomic ■ hypertension ■ blood pressure ■ pregnancy

Very little is known about the activity of the peripheral sympathetic system in normal pregnancy compared with the nonpregnant state. However, using the technique of microneurography,1,2 an increase in the mean frequency of bursts representing multiunit discharge of muscle sympathetic nerve activity (MSNA)3,4 and activity from single units (s-MSNA)5 has been shown to occur during the third trimester in patients with preeclampsia (PE) or pregnancy-induced hypertension (PIH) relative to women with normal pregnancy.

During the third trimester of normal pregnancy, arterial blood pressure tends to rise toward normal nonpregnant levels,6,7 but it is unknown whether central sympathetic drive is involved in this process. The use of indirect measures of sympathetic output, such as changes in hemodynamic variables and circulating catecholamines, has yielded conflicting results in both normal and hypertensive pregnancy.8–13

The present investigation was designed to examine whether central sympathetic vasoconstrictor output to the peripheral vascular bed is altered in normal pregnancy. For this purpose, we studied matched groups of pregnant women prepartum and postpartum with normal pregnancy (NP) and PIH in addition to normotensive nonpregnant (NN) women.

Methods

Subjects

We examined 60 women, ranging in age between 18 and 40 years, between January 1996 and March 2000. They comprised 3 age-matched groups: 21 NP, 21 NN, and 18 PIH. Only white primigravidae were examined, and they were excluded if there was any evidence of secondary hypertension or chronic disease that may influence the autonomic system, such as diabetes mellitus or neurological dysfunction. Otherwise all patients were included in whom it was possible to identify and record single-unit activity. This represented ~60% of the total number of women studied; in the other 40%, it was not possible to obtain a stable recording from a single vasoconstrictor unit.

Patients with PIH were recruited shortly after admission. They were accepted as having PIH if their arterial blood pressure was ≥140/90 mm Hg on at least two separate occasions a minimum of 6
hours apart, they were known to have been normotensive before this time, had no albuminuria (a maximum of ≤300 mg in 24 hours), and had no general systemic abnormality, and they had normal arterial blood pressure by the sixth postpartum week.

Subjects with NP were healthy and were attending routine antenatal clinics. The NN subjects were also healthy women (with an arterial blood pressure ≤130/80 mm Hg) who were recruited from hospital staff or relatives of pregnant women. NP were matched for maternal and gestational age to the group with PIH, and the NN group were age-matched with the other 2 groups. The details of the women are given in Table 1.

All normotensive women were studied while receiving no medical therapy other than iron or vitamins. Of the 18 patients with PIH, 9 had no general systemic abnormality, and they had normal arterial blood pressure, the Valsalva maneuver, and isometric hand-grip exercise. The vasoconstriction function of the activity examined was confirmed by measuring calf vascular resistance (CVR).

The Valsalva maneuver was performed by asking the subjects to exhale into a standard mercury manometer, at a pressure of 40 mm Hg for 15 seconds, while a pneumograph was observed to confirm correct performance of the test. The sympathetic activity increased during the latter part of phase II (blood pressure compensation) and phase III (release of strain and fall in blood pressure) and decreased during phase IV (increase and overshoot of blood pressure).

An electronic discriminator was used objectively to count the spikes of s-MSNA and was quantified as mean frequency of impulses per 100 cardiac beats; this avoided any interference by the length of the cardiac cycle. The bursts of MSNA were identified by previous accepted criteria. Single units (s-MSNA) in the raw action potential neurogram were obtained by adjusting the electrode position. Fast monitor sweep and an online storage oscilloscope were then used to confirm the presence of a single unit by demonstrating consistency in action potential morphology, as previously described. Only vasoconstrictor units were accepted and examined, the criteria of acceptance being appropriate responses to spontaneous changes in arterial blood pressure, the Valsalva maneuver, and isometric hand-grip exercise. The vasoconstriction function of the activity examined was confirmed by measuring calf vascular resistance (CVR).

Statistics
One-way ANOVA with Newman-Keuls multiple post-test comparisons were used to compare data between the different groups.
Student’s t test for paired variables was used to examine changes in variables after delivery, and t test for unpaired variables was used to examine differences between two groups. The relationship between systolic blood pressure and pulse interval was examined using regression analysis. Values of *P* < 0.05 were considered statistically significant. Data are presented as mean ± SEM.

**Results**

The three groups, NN, NP, and PIH, were well matched with the exception of 2 patients in the PIH group who were above average weight. These two patients were not excluded and resulted in a higher (P < 0.01) average body weight in the hypertensive pregnant group (Table 1). As expected, the average indices of arterial blood pressure were significantly greater in PIH than in NP and NN groups. Also, as anticipated from the study design, the blood pressure in 3rd trimester NP subjects was only slightly lower than NN, and the resting heart rate was greater in pregnant women compared with NN. Among the patients with PIH, there were no significant differences in heart rate, mean arterial blood pressure, and sympathetic nerve activity between those who received oral labetalol and those who did not.

As can be seen in Table 1 and Figure 2, the frequency of s-MSNA in NP was significantly greater than in NN, with a 2-fold difference. This frequency was even greater in PIH, with nearly a 4-fold difference compared with NP. Similar differences, although of lesser magnitude, were seen in MSNA between the groups. In addition, CVR was found to be greater in PIH than in the NP and NN groups, and the two groups of pregnant women both had a significantly lower BRS than the NN group.

Follow-up studies were carried out after delivery in 19 NP and 10 PIH women (Table 2). In both groups, the s-MSNA (Figure 3) and MSNA decreased back toward normal values. However, arterial blood pressure and CVR decreased significantly and consistently only in the PIH group, whereas BRS increased significantly in both groups after delivery (Table 2).

**Discussion**

The present investigation has shown for the first time that normal pregnancy is associated with an increase in resting peripheral sympathetic neural discharge having vasoconstrictor properties. The mechanism for this increase could not be explained by changes in body weight or baroreceptor reflex control. This sympathetic hyperactivity occurred to a greater extent in women with PIH than in women with NP.

The increase was found both in single-unit activity and in multunit bursts. The single-unit activity seems to provide a more quantitative estimation of sympathetic discharge than that of multunit bursts and is obtained objectively. Therefore, because the frequency of firing of such units was not affected by other units, it is possible that they reflected the true resting central tone of the peripheral nervous system.

We only examined white women because of reported evidence that race can affect responses of MSNA and only primigravidae to avoid the possibility of a confounding effect.
of multiple pregnancy. The reason for examining women in the 3rd trimester was because during this period in normal pregnancy, the arterial blood pressure and vascular resistance tend to normalize. Because these indices would be similar to a nonpregnant group and also after a normal delivery, significant hemodynamic change would not confound sympathetic measures. To avoid other confounding factors, all studies were undertaken within the same environmental conditions and after a light breakfast with an empty urinary bladder, because visceral distention is known to increase sympathetic activity. In addition, the three groups were matched for age, whereas the pregnant groups were also matched for gestational age to avoid any influence on sympathetic output. Two of the hypertensive patients had preconception obesity resulting in a difference in weight between the two pregnant groups. It is known that obesity can affect resting MSNA; however, if the results are analyzed with these 2 subjects excluded, then there is no change in the overall findings.

The increase in body weight during pregnancy cannot explain the increased sympathetic activity. The frequency of MSNA bursts has been reported to be greater in subjects with obesity, but the weight of such subjects is much greater than in pregnancy and, secondly, our groups (NN and NP) were well matched for body weight. The decrease in sympathetic activity after delivery toward normal values in both the NP and PIH groups, for the same decrease in body weight, is also against body weight being a significant factor. Similarly, the increased sympathetic activity in NP could not be related to baroreceptor reflex compensation, first, because after delivery there was a significant decrease in sympathetic output at a time when there was no significant increase in arterial blood pressure, and, second, because the cardiac baroreceptor reflex sensitivity was reduced in the NP group and recovered after delivery.

Using peroneal nerve microneurography, there are reports of an increase in resting peripheral sympathetic activity in women with PIH or PE compared with women with NP. In one study, comparisons were available between NP and NN; although no significant differences were found between these two groups, measurements were not made in the same subjects before and after delivery. However, in common with previous studies, the present study showed that women with PIH had an increased peripheral sympathetic output relative to women with normal pregnancy. This was additionally confirmed by longitudinal follow-up showing that the sympathetic activity decreased after delivery to values encountered in the NN group.

The present findings have important implications. It is possible to suggest that pregnancy per se results in peripheral sympathetic hyperactivity, the mechanism of which involves central factors. As discussed above, the sympathetic hyperactivity was not related to reflex control, race, or constitutional factors, and it could be the mechanism by which the arterial blood pressure and vascular resistance tend to normalize during the third trimester of normal pregnancy. The excessive increase in sympathetic output found in patients with PIH may by implication be involved in the development of their hypertension. From the published evidence, although limited, it is possible to speculate that the increase in central sympathetic activity in pregnancy is related to hormonal changes, of which there are many. Certainly activation of the renin-angiotensin system is known to occur in pregnancy, and angiotensin II has been shown to increase MSNA. Fasting levels of insulin are raised in the 3rd trimester of pregnancy in women who later develop hypertension, and hyperinsulinemia produces sympathetic activation. Reduction in vasopressin levels has also been reported in pregnancy, and infusion of this hormone has been shown to decrease MSNA. More recently it has been shown that MSNA is greater in young women during the midluteal compared with early follicular phase of the menstrual cycle, when estradiol and progesterone are elevated, and in pregnancy these hormones are additionally elevated. Also, there is
experimental evidence to suggest that central neurotransmitters in the medulla modulate sympathetic output, eg, nitric oxide, but changes in levels during pregnancy and their implications remain to be determined. Finally, one must also consider the hemodynamic changes associated with pregnancy, in particular the increase in blood volume that may be important in increasing sympathetic output and heart rate through afferent sympathetic fibers. Indeed, in accordance with our present findings, a recent study of heart rate variability performed in similar subjects to this study suggested that normal pregnancy had increased sympathetic modulation compared with the nonpregnant state, and that this increase was even greater in hypertensive pregnancy.

In summary, the present investigation has shown that pregnancy is associated with peripheral sympathetic hyperactivity. In women with PIH, this hyperactivity is extreme, but in both situations the levels fall to normal after delivery. There were indications that the mechanisms of this sympathetic hyperactivity involved central factors.

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