Sympathetic Activity and Baroreflex Sensitivity in Young Women Taking Oral Contraceptives

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Background—We tested sympathetic and cardiovagal baroreflex sensitivity during the placebo or “low-hormone” phase (LH) and 2 to 3 weeks later during the “high-hormone” phase (HH) of oral contraceptive (OC) use in 9 women.

Methods and Results—Sympathetic baroreflex sensitivity was assessed by intravenous doses of sodium nitroprusside and phenylephrine and defined as the slope relating muscle sympathetic nerve activity (by microneurography) and diastolic blood pressure. Cardiovagal baroreflex sensitivity was defined as the slope relating R-R interval and systolic blood pressure. No difference was observed for resting muscle sympathetic nerve activity or plasma norepinephrine levels. However, sympathetic baroreflex sensitivity was greater and mean arterial pressure was higher during the LH than in the HH phase. Similarly, cardiovagal baroreflex sensitivity was greater in the LH than in the HH phase.

Conclusions—Sympathetic and cardiovagal baroreflex sensitivities change during the 28-day course of OC use. Furthermore, changes in baroreflex sensitivity with OC differ from changes in baroreflex sensitivity during the normal menstrual cycle. (Circulation. 2000;102:1473-1476.)

Keywords: estrogens • progesterone • blood pressure • nervous system, autonomic

We recently reported that blood pressure regulation by the sympathetic nervous system changes during the menstrual cycle.1 Resting muscle sympathetic nerve activity (MSNA) and sympathetic baroreflex sensitivity, but not cardiovagal baroreflex sensitivity, were greater during the midluteal (high hormone) phase compared with the early follicular (low hormone) phase of the menstrual cycle.

Our goal in the present study was to extend these observations to women taking oral contraceptives (OC). We compared resting MSNA, sympathetic baroreflex sensitivity, and cardiovagal baroreflex sensitivity in young women during the placebo or “low hormone” (LH) phase of OC use and during the active OC phase (“high hormone”; HH). We hypothesized that our results would parallel our previous findings, ie, resting MSNA and sympathetic baroreflex sensitivity would be greater when women were taking exogenous estrogen and progesterin than when taking the placebo.

Methods

Subjects

The Institutional Review Board approved all procedures. Nine women were recruited and gave written consent. Subjects were young (30±2 years), healthy (body mass index, 24.2±1.0 kg/m²) nonsmokers who had not taken medications except monophasic OC, which provided 30 to 35 μg of ethinyl estrogen and low-dose progesterin for 21 days and placebo for 7 days.

Experimental Protocol

Subjects were studied twice, once during the LH phase (4 to 5 days after starting placebo pill, 3 to 6 days after onset of menstruation) and once during the HH phase of OC use (17 to 20 days after starting the ethinyl estrogen-progestin pills). The order of testing was counterbalanced.

Subjects were placed in the supine position, and a catheter was placed in an antecubital vein for drug injections. Heart rate was determined from an ECG, and beat-by-beat arterial pressure was measured using a Finapres device (Model 2300, Ohmeda). Blood pressure cuffs were placed around the ankle and thigh for calf blood flow measurements using venous occlusion plethysmography.2 Calf vascular resistance was calculated as CVR=MAP/CBF (where CVR indicates calf vascular resistance; MAP, mean arterial pressure; and CBF, calf blood flow) to provide an estimate of regional vascular resistance. Sixty minutes after placement of the intravenous catheter, a 10 mL sample of blood was drawn to measure catecholamines. Samples were frozen for later analysis by high performance liquid chromatography. After an acceptable nerve recording had been found, resting calf blood flow was measured for 3 minutes; this was followed by a 5-minute recording of resting MSNA. After resting measurements, 2 baroreflex sensitivity tests were performed.

Measurements

MSNA was recorded via microneurography from the peroneal nerve, amplified, filtered, and analyzed as previously described.3 MSNA was quantified as total integrated “activity,” which was defined as the summed area of bursts, and normalized by assigning the largest sympathetic burst under resting conditions an amplitude of 1000. To assess baroreflex sensitivity, MSNA and heart rate were measured during the arterial pressure changes induced by a bolus injection of 100 μg of sodium nitroprusside followed 1 minute later by 150 μg of phenylephrine.4 After a 20-minute recovery period, a second baroreflex test was performed. The results from the 2 trials were combined to provide a single data set for the determination of baroreflex sensitivity.

Data acquisition and analysis were identical to our previous study.1 Briefly, sympathetic baroreflex sensitivity was determined by...
the relation between MSNA and diastolic blood pressure (DBP) during drug infusions. To perform a linear regression between MSNA and pressure, values for MSNA from both baroreflex trials were first combined and then pooled over 3 mm Hg pressure ranges. Any heartbeat not followed by a burst was assigned a total integrated activity of zero. The relation between R-R interval and systolic blood pressure (SBP) determined cardiovagal baroreflex sensitivity during drug infusions. Values for the R-R interval from both baroreflex trials were first combined and then pooled over 2 mm Hg increments during the baroreflex trial.

Statistical Analysis
All statistical analyses were performed using SAS version 6.12 (SAS Institute, Inc). Baseline variables were compared by paired t tests. Sympathetic and cardiovagal baroreflex relations were analyzed by multivariate linear regression models with repeated measures. Weighted linear regressions (by number of beats in each DBP bin) between MSNA and DBP were performed to assess sympathetic baroreflex sensitivity, and weighted linear regressions (by number of beats in each SBP bin) between R-R interval and SBP were performed to assess cardiovagal baroreflex sensitivity. P<0.05 was considered significant. Values are reported as means±SEM.

Results
Baseline values measured during the 2 phases of OC use are presented in the Table. No significant differences were observed for heart rate, SBP, calf vascular resistance, resting MSNA, or norepinephrine or epinephrine levels. However, DBP and mean arterial pressure were significantly higher during the LH phase than in the HH phase.


diastolic blood pressure (mm Hg)

Figure 1. A, Data from representative subject during sympathetic baroreflex sensitivity test. Dashed line represents weighted linear regression during LH, and solid line represents weighted linear regression during HH. B, Comparison of slopes for all subjects (r²=0.74 to 0.90). Dashed line represents mean±SEM (P<0.01).

Cardiovagal Baroreflex Sensitivity
An example of the data obtained during the cardiovagal baroreflex test from one subject is displayed in Figure 2A, and a comparison of slopes for all subjects during the LH and HH phases is presented in Figure 2B. Cardiovagal baroreflex sensitivity was significantly greater during the LH than the HH phase of OC use (P=0.017).

Discussion
To our knowledge, these are the first sympathetic nerve recordings in women that examine sympathetic outflow during the course of OC use. The major findings in this study are as follows: (1) resting blood pressure is higher, but MSNA and heart rate are similar at rest in the LH phase of OC use when compared with the HH phase, and (2) sympathetic and cardiovagal baroreflex sensitivities change during the 28-day cycle of monophasic OC use. Specifically, symp-
women on OC; this difference was not observed in normally cycling women. However, reduced peripheral vascular tone should be countered by an increase in baseline sympathetic activity unless the baroreflex is reset. We did not observe a significant increase in baseline MSNA or plasma norepinephrine levels in the present study. Thus, it seems that baroreflex sensitivity was reset to a lower blood pressure during the HH phase of OC use. Most likely, resetting occurred as a secondary response to changes in peripheral vascular resistance induced by the exogenous hormones. In contrast, we did not observe a resetting of the sympathetic baroreflex curves in normally cycling women.1 Taken together, these data suggest that exogenous hormones cause a central resetting of baroreflex sensitivity that may not occur with endogenous forms of the hormones.

Second, the ratio between estrogen and progesterone may determine baroreceptor function. Evidence for this possibility stems from animal studies suggesting estrogen enhances sympathetic baroreflex sensitivity7 and progesterone reduces sympathetic baroreflex sensitivity.8 Our previous data from normally cycling women suggested that estrogen augmented sympathetic baroreflex sensitivity and that progesterone antagonized this response in young women.4 However, we did not find a strong relationship between the absolute estrogen-progesterone ratio and baroreflex sensitivity in normally cycling women. With OC, it is not possible to determine the estrogen-progesterone ratio because of the complex metabolic pathways involved in the degradation of exogenous hormones and because the relative potency of the exogenous hormones may differ from the endogenous forms.

Third, it is also possible that the observed changes in baroreflex function with various forms of estrogen and progesterone are secondary to the effects of these hormones on other physiological systems. For example, plasma volume decreases 8% from the early follicular phase to the midluteal phase in normally cycling women, but no change in plasma volume is observed during the course of OC use.9 It has been suggested that this degree of plasma volume change could lead to increased baroreflex sensitivity.8 In addition, estrogen and progesterone could indirectly alter baroreflex sensitivities by altering arterial distensibility,10 thus changing the impact of pressure fluctuations on baroreceptor firing. Changes in baroreflex sensitivities may have occurred to maintain blood pressure in response to changes in other physiological systems during the course of the menstrual cycle or OC use.

In summary, these studies suggest that endogenous and exogenous forms of estrogen and progesterone differentially modify the mechanisms by which blood pressure is regulated in women. The implications of these changes in baroreflex function with OC use on blood pressure regulation are unknown. Depending on a variety of complex physiological interactions, these changes might either contribute to or protect women from conditions like orthostatic intolerance or hypertension in the long term. In this context, the impact of female reproductive hormones and baroreflex function on these conditions awaits further study.

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