Sympathetic Activity and Baroreflex Sensitivity in Young Women Taking Oral Contraceptives

Christopher T. Minson, PhD; John R. Halliwill, PhD; Tamica M. Young, BA; Michael J. Joyner, MD

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.)

Key Words: estrogens • progesterone • blood pressure • nervous system, autonomic

W e 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 informed consent. Subjects were young (30±2 years), healthy (body mass index, 24.2±1.0 kg/m²) nonsmokers who had not taken medications except monophase 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-progesterin 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 Cardiac output 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

**References**


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 \( \pm \) 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. Resting MSNA Activity/min 1199 \( \pm \) 271 1383 \( \pm \) 303 0.31
Burst/min 11.0 \( \pm \) 1.4 11.8 \( \pm \) 2.7 0.67
Norepinephrine, pg/mL 230 \( \pm \) 46 298 \( \pm \) 91 0.16
Epinephrine, pg/mL 15.4 \( \pm \) 4.4 14.0 \( \pm \) 3.8 0.75

**Sympathetic Baroreflex Sensitivity**

An example of the data obtained from one subject is displayed in Figure 1A, and a comparison of slopes from all subjects during both phases is presented in Figure 1B. In the representative subject, resting DBP was higher in the LH phase, despite a resting MSNA similar to that in the HH phase. Furthermore, baroreflex sensitivity was greater (more negative slope) during the LH phase than in the HH phase. Across all subjects, baroreflex slopes were more negative in the LH phase, indicating greater baroreflex sensitivity during the LH than in the HH phase (\( P < 0.01 \)). Changes in DBP from baseline during drug infusions were similar during both phases studied, indicating that the stimulus for the baroreflex sensitivity test was similar in both phases.

**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, sym-
First, differences in the physiological effects or potency of exogenous versus endogenous forms of estrogen or progesterone on baroreflex function may contribute to the different observations in our 2 studies. Combined OC agents deliver pharmacological levels of estrogens that exhibit 6 to 10 times greater when estrogen and progesterone levels were elevated in the LH phase (placebo pills) than the HH phase during the course of OC use.5 It has been suggested that this degree of plasma volume change could lead to increased baroreflex sensitivity.9 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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