Hormonal contraceptives are used by ≈80% of women in the United States during their lifetime, not only for the prevention of unintended pregnancy but also for medical indications, such as menorrhagia, dysmenorrhea, and sex hormone imbalances.1,2 Hormonal contraceptives, often prepared as ethinyl estradiol and progestin combinations, are known to have unfavorable effects on the cardiovascular system with chronic use.2 In addition to increased risk of arterial and venous thrombosis, one of the most common consequences is increased blood pressure with an elevated risk for the development of hypertension.3 With long-term use of hormonal contraceptives sometime during their life, the influence of combined oral contraceptives (OCs) on MSNA and systemic hemodynamics remains equivocal. The goal of this study was to determine whether women taking OCs have altered MSNA and hemodynamics (cardiac output and total peripheral resistance) at rest during the placebo phase of OC use compared with women with natural menstrual cycles during the early follicular phase. We retrospectively analyzed data from studies in which healthy, premenopausal women (aged 18–35 years) participated. We collected MSNA values at rest and hemodynamic measurements in women taking OCs (n=53; 25±4 years) and women with natural menstrual cycles (n=74; 25±4 years). Blood pressure was higher in women taking OCs versus those with natural menstrual cycles (mean arterial pressure, 89±1 versus 85±1 mm Hg, respectively; P=0.01), although MSNA was similar in both groups (MSNA burst incidence, 16±1 versus 18±1 bursts/100 heartbeats, respectively; P=0.19). In a subset of women in which detailed hemodynamic data were available, those taking OCs (n=33) had similar cardiac output (4.9±0.2 versus 4.7±0.2 L/min, respectively; P=0.47) and total peripheral resistance (19.2±0.8 versus 20.0±0.9 U, respectively; P=0.51) as women with natural menstrual cycles (n=22). In conclusion, women taking OCs have higher resting blood pressure and similar MSNA and hemodynamics during the placebo phase of OC use when compared with naturally menstruating women in the early follicular phase. (Hypertension. 2015;66:590-597. DOI: 10.1161/HYPERTENSIONAHA.115.05179.)
In considering mechanisms for potential influences of OCs on blood pressure regulation, it is important to consider the effect of sex hormones on the relationships between MSNA and hemodynamic variables. Hart et al.\textsuperscript{14} reported that young premenopausal women (a cohort including some individuals taking OCs) did not demonstrate a relationship between MSNA and mean arterial pressure (MAP) or MSNA and total peripheral resistance (TPR). Conversely, in young men and older postmenopausal women, there is a positive correlation between MSNA and MAP, as well as MSNA and TPR.\textsuperscript{15} These findings suggest that endogenous female sex hormones (estrogen and progesterone) influence blood pressure regulation and their absence may modulate hypertension risk. In this context, exogenous female sex hormones in the form of OCs could potentially alter these relationships and influence blood pressure regulation.

With this information as a background, our goal was to evaluate the effects of OCs on MSNA, MAP, TPR, and cardiac output (CO), as well as the relationships that exist between these variables in OC users. We hypothesized that MSNA and hemodynamics would be altered in women taking OCs, as would the relationships between MSNA and hemodynamic variables, in comparison with women with natural menstrual cycles who were not taking OCs. To minimize potential confounding effects of hormone fluctuations across the menstrual cycle, we studied women in either the early follicular (ie, the low-hormone) phase of the menstrual cycle or the placebo cycle, we studied women in either the early follicular (ie, the low-hormone) phase of the menstrual cycle or the placebo phase of OC use. We reasoned that this approach would give us comparable baselines between the 2 groups.

**Methods**

**Study Design Overview**

Data were retrospectively pooled from previous MSNA studies that took place at the following institutions: (1) Mayo Clinic, Rochester, MN\textsuperscript{16–19}; (2) Michigan Technological University, Houghton, MI\textsuperscript{8,11,20–24}; (3) Institute for Exercise and Environmental Medicine at Texas Health Presbyterian Hospital Dallas, and University of Texas Southwestern Medical Center, Dallas, TX\textsuperscript{9}; and (4) University of Oregon, Eugene, OR.\textsuperscript{9} These studies followed similar protocols with respect to microneurography technique and MSNA analysis. All studies were approved by their respective institutional review boards.

**Subjects**

Because the risk of adverse events with OC use increases with age, and use is not encouraged in women who are >35 years and have cardiovascular risk factors (eg, smoking, obesity, and diabetes mellitus),\textsuperscript{25} we restricted our study participants to premenopausal women aged between 18 and 35 years. We initially identified 166 women to be included in this review. Individuals were excluded because of unknown OC status (n=8), age >35 years (n=7), a baseline data recording <5 minutes in duration (n=2), and duplicate subjects from different studies (n=12), in which case the first data recording was used or the most complete data file remained in our analysis. Four women taking nonoral forms of contraception (intrauterine device, patch, ring, implant), n=1; transdermal patch, n=1; vaginal ring, n=2) were excluded, as would the relationships between MSNA and hemodynamic variables, in comparison with women with natural menstrual cycles who were not taking OCs. To minimize potential confounding effects of hormone fluctuations across the menstrual cycle, we studied women in either the early follicular (ie, the low-hormone) phase of the menstrual cycle or the placebo phase of OC use. We reasoned that this approach would give us comparable baselines between the 2 groups.

**Data Analysis**

Data were digitized from microneurography recordings because of the varying influences of estrogen and progesterone on MSNA\textsuperscript{7,9,11,12} and cardiovascular factors, such as endothelial function\textsuperscript{26–30} across the menstrual cycle and during the different phases of OC use. In addition, both endogenous estrogen and progesterone concentrations are relatively low during these stages, in contrast to the luteal phase, during which plasma estrogen concentrations are moderate and plasma progesterone concentrations are high.\textsuperscript{31–33} This is important as progesterone may antagonize estrogen’s effects on the vasculature\textsuperscript{34} or potentially have an independent influence on MSNA.\textsuperscript{14,35}

**Study Protocol Standardization**

All subjects provided written informed consent before study participation. Subjects refrained from alcohol, caffeine, and exercise for 12 to 24 hours before the study. Subjects who were studied in the morning underwent an overnight fast, and subjects who were studied in the afternoon underwent a 3-hour fast before participation (the vast majority of studies were conducted in the morning). Baseline measurements were collected across 5 to 10 minutes of recording after the subject had been resting quietly in the supine position for ≈30 minutes.

**Measurement of Variables of Interest**

Data pertaining to medical history and OC status were collected at the time of study screening. Blood pressure was measured continuously using a brachial artery catheter\textsuperscript{4–10} or a noninvasive finger photoplethysmography cuff\textsuperscript{8,9,11,20–24} to obtain a beat-to-beat blood pressure waveform. To establish baseline blood pressure for subjects in whom finger photoplethysmography was used, a brachial cuff pressure measurement was completed (an average of 3 measurements is reported). Heart rate was monitored using a standard 3-lead ECG. Multitri spit MSNA was recorded by placing a tungsten microelectrode in the peroneal nerve at the fibular head. A reference electrode was placed subcutaneously ≈3 cm from the recording electrode. The recorded signal was amplified 80000- to 100000-fold, band-pass filtered (700–2000 Hz), rectified, and integrated (resistance–capacitance integrator circuit, time constant 0.1 s) by a nerve traffic analyzer.\textsuperscript{16} MSNA variables are expressed as burst frequency (bursts/min) and burst incidence (bursts/100 heartbeats). Stroke volume (SV) was derived in subjects whose blood pressure was measured via a brachial artery catheter (n=55) using Modelflow analysis (Beatscope, Finapres) and reported in milliliters. CO was calculated as SV×heart rate/1000 and expressed in liters per minute, and TPR as MAP/CO and expressed in millimeter of mercury per liter per minute.

Blood samples were collected in a subset of women, and plasma norepinephrine and epinephrine concentrations were reported when available.
Statistical Analysis

Group demographics and data are reported as mean±SE. Demographic variables from the 2 groups were compared using the Student t test (SigmaPlot 12.0, Systat Software, San Jose, CA). MSNA, all hemodynamic variables, catecholamines, and sex hormone levels were also compared using the Student t test. Pearson correlation analysis was utilized to determine the correlation coefficient (r) between MSNA and the hemodynamic variables of MAP, TPR, and CO. A calculated P value of ≤0.05 was considered significant.

Results

Seventy-four women with natural menstrual cycles (non-OC) and 53 women taking OCs were included in our analysis. Demographic data for both groups are summarized in Table 1. Age (P=0.60) and body mass index (P=0.11) were not different between the 2 groups.

Group data for baseline blood pressure (brachial cuff or brachial arterial catheter), heart rate, and MSNA are shown in Table 2. Systolic (P<0.001), diastolic (P=0.05), and mean (89±1 versus 85±1 mm Hg, respectively; P=0.01) arterial pressures were greater in women taking OCs versus non-OC women. Pulse pressure (P<0.01) was also higher in women taking OCs. Heart rate was not different between the 2 groups (P=0.69). There were no significant differences in MSNA burst frequency (10±1 versus 11±1 bursts/min, respectively; P=0.25) or MSNA burst incidence (16±1 versus 18±1 bursts/100 heartbeats, respectively; P=0.19) between OC and non-OC women (Figure 1).

SV, CO, and TPR were obtained in a subset of women in whom continuous blood pressure was measured using an intra-arterial brachial pressure transducer (n=22 for non-OC women and n=33 for OC women). All variables were found to be similar between the 2 groups (SV: P=0.94; CO: P=0.47; TPR: P=0.51; Table 3). Of note, in this subset of women, age was different (27±1 versus 24±1; non-OC versus OC, respectively; P=0.03) and MAP was similar (93±2 versus 91±2 mm Hg; P=0.052) in the groups (Table S1 in the online-only Data Supplement). By contrast, MSNA was different (22±2 versus 16±2 bursts/100 heartbeats; non-OC versus OC, respectively; P=0.03), but similar after adjusting for age (P=0.11).

Plasma norepinephrine (P=0.65) and epinephrine (P=0.74) levels, available in 22 non-OC women and 29 OC women, were not different between the 2 groups (Table 4). No relationships existed between MSNA burst incidence and norepinephrine or epinephrine. Plasma estradiol and progesterone levels, available in 43 non-OC women and 19 OC women, were not different between the 2 groups (P=0.65 and P=0.09, respectively).

The relationship between MSNA burst incidence and MAP is shown in Figure 2. There was a weak, but significant, positive correlation between these 2 variables in women with natural menstrual cycles (r=0.27; R²=0.073; P=0.02), whereas there was no relationship between these variables in women taking OCs (r=0.21; R²=0.044; P=0.13). The relationships between MSNA and CO and MSNA and TPR are shown in Figure 3. There was no correlation between MSNA and CO in either group of women (non-OC: r=-0.09, R²=0.008; P=0.69; OC: r=-0.05, R²=0.003; P=0.77) nor was there any correlation between MSNA and TPR in either group (non-OC: r=0.11, R²=0.012, P=0.63; OC: r=0.21, R²=0.044, P=0.23). Similar trends were observed between the associations of MSNA burst frequency and MAP, CO, and TPR.

Discussion

The major new findings of the present study are that MSNA, CO, and TPR at rest did not differ between women with natural menstrual cycles and women who take OCs during the low-hormone phase of the menstrual cycle and placebo phase of OC use. Our present analysis also provides novel mechanistic insight into sympathetic regulation of blood pressure in young women by reporting on the associations between MSNA and the hemodynamics of MAP, CO, and TPR in OC users and naturally cycling women. We saw evidence of divergent relationships between blood pressure and MSNA in normal cycling women versus women taking OCs. In addition, MSNA was similar between the 2 groups; however, blood pressure was higher in women taking OCs. Because OCs are known to activate the renin–angiotensin–aldosterone system, our findings suggest that OC use limits the ability of baroreceptors to lower MSNA in the face of increased blood pressure. We saw no significant relationships between MSNA and CO or MSNA and TPR in either group. As others have previously reported,4,5 we observed that blood pressure was significantly higher in OC users versus OC nonusers.
OC-induced hypertension has been reported since the 1960s with the development of combined OCs. These first-generation OCs contained much higher concentrations of estrogen (150 μg), in combination with a progestin, compared with more recent formulations (20–35 μg of estrogen plus a progestin); however, OCs containing lower estrogen concentrations may still cause increases in blood pressure. Some of the fourth-generation OCs, such as Ocella, Yaz, and Yasmin, have the potential to counteract blood pressure elevation, as they contain the progestin drospirenone, which has antimineralocorticoid activity. In women who take these OC formulations, blood pressure does not change or may slightly decrease. In our cohort, 6 women were taking such OCs at the time of being studied, and indeed, there was a tendency for women taking drospirenone-containing OCs to have a lower MAP than women taking other types (n=46) of OCs (83±3 versus 90±1 mm Hg; \( P = 0.06 \)). In addition, in our data set, a subanalysis by OCP formulation (monophasic, diphasic, versus triphasic) showed no differences in blood pressure, MSNA, and heart rate, suggesting that these OCP types do not have differential effects in this particular group of women (Table S2). SV was significantly greater in women taking triphasic OCPs than in women taking monophasic OCPs (\( P < 0.05 \)), but there were no significant differences in CO and TPR.

Our study did not examine the effects of hormonal contraceptives administered through nonoral routes. The vaginal ring contraceptive, for example, has been associated with elevated diastolic and mean blood pressures; however, its effect on the sympathetic nervous system has never been studied. We also did not include women who took progestin-only contraceptive formulations in our analysis. Progestin-only pills have not been associated with increased blood pressure in normotensive women, and it is unknown whether they would be associated with changes in MSNA.

We hypothesized that MSNA at rest would be influenced by OC use for 2 main reasons. First, MSNA is greater in young men and older postmenopausal women than in young women, suggesting an inhibitory influence of female sex hormones on tonic levels of sympathetic activity. Higher concentrations of endogenous female sex hormones, particularly estrogen and progesterone, are thought to be protective to the cardiovascular system and reduce a young woman’s risk of hypertension. Androgens can also influence this risk and should also be taken into consideration, as evidence suggests that elevated androgen levels in women may be detrimental to the cardiovascular and endocrine systems. Simultaneously and somewhat paradoxically as noted above, it is known that OC use increases an individual’s risk for hypertension. Female reproductive hormones (particularly estrogens) can promote both systemic vasodilation via enhanced nitric oxide synthesis (which would lower blood pressure) and expand plasma volume (which could increase blood pressure). OCs (combined estradiol and progesterone formulations) also are known to upregulate the renin–angiotensin–aldosterone system to increase angiotensinogen, angiotensin II, and aldosterone levels, as well as plasma renin activity and renal vascular resistance, resulting in increased blood pressure. Progesterone alone, depending on the type of vessel and strength of exposure, may cause vasoconstriction or vasodilation. For example, physiological concentrations of progesterone can oppose estrogen’s vasodilating effects on the endothelium when measured via flow-mediated dilation. It is important to note that synthetic progestins have activity not only at the progesterone receptor

### Table 3. Systemic Hemodynamic Variables in Available Individuals

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Non-OC (n=22)</th>
<th>OC (n=33)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke volume, mL</td>
<td>80±3</td>
<td>80±2</td>
<td>0.94</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.7±0.2</td>
<td>4.9±0.2</td>
<td>0.47</td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>20.0±0.9</td>
<td>19.2±0.8</td>
<td>0.51</td>
</tr>
<tr>
<td>resistance, mm Hg/L per minute</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values represent mean±SEM. OC indicates oral contraceptive.

### Table 4. Plasma Catecholamine Levels in Available Individuals

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Non-OC (n=22)</th>
<th>OC (n=29)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>186±17</td>
<td>173±20</td>
<td>0.65</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>25.7±4.2</td>
<td>24.1±2.5</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Values represent mean±SEM. OC indicates oral contraceptive.
but also at other steroid receptors to have androgenic, glucocorticoid, antiandrogenic, and antimineralocorticoid effects. A progestin’s influence on blood pressure regulation will be highly dependent on its composition and concentration. As discussed above, OCs containing the progestin drospirenone, which has high antimineralocorticoid activity, will promote urinary loss of water and sodium and thereby reduce blood pressure.49 Taken together, the volume expanding effects of OCs and the resultant effects on blood pressure seem to predominate.

In contrast to our findings, we initially hypothesized that resting MSNA might be different between OC users and nonusers was based on evidence that MSNA fluctuates across the menstrual cycle. Specifically, our rationale for this hypothesis was that MSNA is often higher in the midluteal phase of the menstrual cycle (when both endogenous

Figure 2. Correlation analysis of the relationship between muscle sympathetic nerve activity (MSNA) and mean arterial pressure in women with natural menstrual cycles (non–oral contraceptive [non-OC], left, n=74) and women taking OC (right, n=53).

Figure 3. Correlation analyses of the relationships between (A) muscle sympathetic nerve activity (MSNA) and cardiac output and (B) MSNA and total peripheral resistance in women with natural menstrual cycles (non–oral contraceptive [non-OC], left, n=33) and women taking OC (right, n=22). Analysis only includes women in whom blood pressure was measured via brachial artery catheter.
estrogen and progesterone concentrations are relatively high) in normally menstruating women, a finding that seems to be partially dependent on endogenous levels of estradiol and progesterone. However, previous data on the influence of OCs on MSNA have been conflicting. With the exception of 1 report, studies have noted no difference in MSNA at rest between the placebo pill phase and active pill phase of OC use, which is in agreement with reports that blood pressure does not decrease during the placebo phase of OC use. This suggests that MSNA during the placebo phase does not equate to MSNA reported during the early follicular phase of the natural menstrual cycle. Middlekauff et al investigated ambulatory blood pressure, MSNA levels, and baroreceptor control of MSNA in women both on and off OCs across a 28-day cycle. Although it appears that there may be differences in MSNA between women taking OCs during the active pill phase and women with natural menstrual cycles during the midluteal phase, this possibility has not been studied directly. In addition, although it is well documented that blood pressure increases with the initiation of OC use, it is yet to be determined whether MSNA, measured directly, is altered when a woman with a natural menstrual cycle begins taking an OC.

When we initiated this analysis, we hypothesized that both blood pressure and MSNA would be higher in OC users in comparison with women with normal menstrual cycles. The fact that blood pressure was higher while MSNA was similar raises the possibility that OC use limits the ability of baroreflexes to suppress sympathetic activity. This also suggests that OC use alters the overall relationship between blood pressure and MSNA. In this context, an acute increase in diastolic or mean arterial blood pressure of 3 to 5 mm Hg is usually experimentally sufficient to abolish MSNA in healthy young subjects. Thus, although MSNA did not differ between OC users and nonusers, it was perhaps unexpectedly high in women taking OCs given the differences in arterial pressure.

In our previous study, Hart et al determined that MSNA, CO, and TPR were different between young premenopausal women and older postmenopausal women, and the relationships between these variables were different between groups. Specifically, CO was found to be lower in postmenopausal women, whereas MSNA and TPR were greater. Also, positive relationships existed between MSNA and MAP, as well as MSNA and TPR, in postmenopausal women, whereas there were no relationships between these variables in young women. Importantly, these relationships observed in postmenopausal women were similar to the relationships in young men, highlighting the potential effect of female sex hormones. Earlier studies suggest that endogenous female sex hormones may modulate the relationship between these cardiovascular factors and decrease a young woman’s susceptibility to hypertension development. However, the group of young women in the study by Hart et al composed of women with both natural menstrual cycles (n=7) and taking OCs (n=11).

In the present study, we found no association between MSNA and CO or TPR in either group. Although we noted a positive relationship between MSNA and MAP in women with normal menstrual cycles, the correlative value was weak (r=0.27; P=0.02), and we are hesitant to draw any conclusions based on this observation. Therefore, in light of these current findings, the overall conclusion from the study by Hart et al would not be dramatically altered. That is, it is reasonable to conclude from both reports that, in young women with natural menstrual cycles, large individual differences in MSNA do not result in drastic changes in MAP.

Limitations
There are several limitations to this study. First, because of methodological differences between sites, detailed hemodynamic variables were unattainable for all women in our cohort. The subset of women in which hemodynamic variables were available had different characteristics than the overall group, including differences in age and MSNA, but no differences in blood pressure. However, MSNA did not differ when adjusted for age.

Second, methodological consistency related to microneurography may be difficult to control across different studies within institutions. However, all laboratories contributing material to this study are highly experienced and follow what might be called a standard technique for human microneurography, and thus, the intrasubject repeatability of the technique is high (a statistical comparison of participant baseline characteristics, blood pressures, and MSNA levels by institution is provided in Table S3).

Third, the women in this study were taking a variety of OC formulations, and because of the retrospective nature of this project, we were unable to control for this variable. However, studying a sample of women taking a single type of OC may be problematic when generalizing results to a wider population. In addition, the use of the same OC across all individuals does not guarantee that plasma estrogen and progesterone levels would be homogenous among the women, as pharmacokinetics and pharmacodynamics related to OCs may differ between individuals. Importantly, a subanalysis of women on the 3 main formulations of OCs in this study showed no major effects on blood pressure or MSNA. Other factors unknown to us about our sample include duration of OC use and reason for OC use, which could potentially input selection bias into our data set. Finally, the women in the current study were all relatively lean, healthy whites so our findings may not extend to women of different races. Obesity and other metabolic or endocrine disorders might alter how endogenous and exogenous hormones influence the relationships investigated in these studies.

Perspectives
Women taking OCs have higher blood pressure than women with natural menstrual cycles who are not taking OCs. MSNA at rest, as well as CO and TPR, is similar between these 2 groups of women. The fact that MSNA was not lower in the face of elevated blood pressure in OC users raises questions about how exogenous hormones influence neurovascular control of the circulation perhaps via activation of the renin–angiotensin–aldosterone system by OCs. In addition, our results were observed during the placebo phase of OC use and the early follicular phase of the menstrual cycle. Thus, much remains unknown about the interactions among exogenous and endogenous female sex hormones, MSNA, and hemodynamics across all phases of the menstrual cycle or OC use.
In addition, information on OC use (past and present), type, and duration is frequently not reported and taken into consideration when studying MSNA and blood pressure regulation. These observations highlight the need to include information on sex, hormone, and reproductive factors in research studies and the importance of sex-specific physiology, treatment, and health outcomes.

**Acknowledgments**

We thank Michael Mozer for his assistance in data analysis. The contents of this work are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health. The views, opinions, and findings contained in this article are those of the authors and should not be construed as an official Department of the Army position, or decision, unless so designated by other official documentation. Approved for public release; distribution unlimited.

**Sources of Funding**

This work was supported by the American Heart Association (AHA) 14PRE18040000 and NCATS UL1 TR000135 (R.E. Harvey); NIH HL118154 and AG38067 (J.N. Barnes). 14PRE18040000 and NCATS UL1 TR000135 (R.E. Harvey); AHA Funding Sources: NIH HL118154 and AG38067 (J.N. Barnes).

**References**


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Hypertension. 2015;66:590-597; originally published online June 22, 2015; doi: 10.1161/HYPERTENSIONAHA.115.05179

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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Oral contraceptive use, muscle sympathetic nerve activity, and systemic hemodynamics in young women

Ronee E. Harvey¹, Emma C. Hart², Nisha Charkoudian³, Timothy B. Curry¹, Jason R. Carter⁴, Qi Fu⁵, Christopher T. Minson⁶, Michael J. Joyner¹, Jill N. Barnes¹

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Running title: Oral contraceptives, MSNA & hemodynamics in women

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Table S1. Comparison of Individuals in Whom Hemodynamic Variables Were Available

<table>
<thead>
<tr>
<th>Demographic/Measurement</th>
<th>Non-OC (n=22)</th>
<th>OC (n=33)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>27 ± 1</td>
<td>24 ± 1</td>
<td>0.02*</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>23 ± 1</td>
<td>23 ± 1</td>
<td>0.64</td>
</tr>
<tr>
<td>Heart rate, beats/minute</td>
<td>60 ± 2</td>
<td>61 ± 1</td>
<td>0.50</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>131 ± 3</td>
<td>130 ± 2</td>
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<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>73 ± 2</td>
<td>71 ± 1</td>
<td>0.40</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>93 ± 2</td>
<td>91 ± 2</td>
<td>0.52</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>58 ± 1</td>
<td>58 ± 2</td>
<td>0.88</td>
</tr>
<tr>
<td>MSNA burst frequency, bursts/minute</td>
<td>14 ± 2</td>
<td>10 ± 1</td>
<td>0.05*</td>
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<tr>
<td>MSNA burst incidence, bursts/100 heartbeats</td>
<td>22 ± 2</td>
<td>16 ± 2</td>
<td>0.13, adjusted for age 0.03*</td>
</tr>
</tbody>
</table>

Mean ± SEM. MSNA, muscle sympathetic nerve activity. OC, oral contraceptive.
### Table S2. Comparison of Women by OC Type.

<table>
<thead>
<tr>
<th>Demographic/Measurement</th>
<th>Monophasic (n=31)</th>
<th>Biphasic (n=3)</th>
<th>Triphasic (n=18)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>26 ± 1</td>
<td>24 ± 2</td>
<td>23 ± 1</td>
<td>0.17</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23 ± 1</td>
<td>21 ± 2</td>
<td>23 ± 1</td>
<td>0.44</td>
</tr>
<tr>
<td>Heart rate, beats/minute</td>
<td>63 ± 1</td>
<td>64 ± 3</td>
<td>60 ± 2</td>
<td>0.47</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>123 ± 2†</td>
<td>119 ± 5‡</td>
<td>128 ± 5§</td>
<td>0.53</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>72 ± 1†</td>
<td>74 ± 6‡</td>
<td>72 ± 2§</td>
<td>0.86</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>89 ± 1</td>
<td>89 ± 5</td>
<td>91 ± 3</td>
<td>0.75</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>51 ± 2</td>
<td>45 ± 2</td>
<td>57 ± 4</td>
<td>0.15</td>
</tr>
<tr>
<td>MSNA burst frequency, bursts/minute</td>
<td>10 ± 1</td>
<td>12 ± 5</td>
<td>10 ± 1</td>
<td>0.77</td>
</tr>
<tr>
<td>MSNA burst incidence, bursts/100 heartbeats</td>
<td>16 ± 1</td>
<td>19 ± 6</td>
<td>16 ± 2</td>
<td>0.87</td>
</tr>
</tbody>
</table>

### Comparison of Hemodynamics in Available Individuals by OC Type

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Monophasic (n=19)</th>
<th>Biphasic (n=2)</th>
<th>Triphasic (n=11)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke volume, mL</td>
<td>77 ± 2</td>
<td>70 ± 9</td>
<td>87 ± 3</td>
<td>0.01*</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.8 ± 0.2</td>
<td>4.4 ± 0.7</td>
<td>5.3 ± 0.4</td>
<td>0.35</td>
</tr>
<tr>
<td>Total peripheral resistance, mmHg/L/min</td>
<td>19.4 ± 1.1</td>
<td>20.4 ± 4.8</td>
<td>18.7 ± 1.5</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Mean ± SEM. MSNA, muscle sympathetic nerve activity. OC, oral contraceptive.
†n=19 measured via brachial artery catheter, n=12 measured via brachial cuff
‡n=2 measured via brachial artery catheter, n=1 measured via brachial cuff
§n=11 measured via brachial artery catheter, n=7 measured via brachial cuff
One individual was excluded from this analysis due to unknown OC type.
<table>
<thead>
<tr>
<th>Demographic/Measurement</th>
<th>Institution 1 (n=35)</th>
<th>Institution 2 (n=22)</th>
<th>Institution 3 (n=9)</th>
<th>Institution 4 (n=8)</th>
<th>Significantly Different (p&lt;0.05) Pairwise Comparisons*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>23 ± 1</td>
<td>27 ± 1</td>
<td>28 ± 1</td>
<td>26 ± 1</td>
<td>1 vs. 2,3</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24 ± 1</td>
<td>23 ± 1</td>
<td>23 ± 1</td>
<td>23 ± 1</td>
<td>-</td>
</tr>
<tr>
<td>Heart rate, beats/minute</td>
<td>62 ± 1</td>
<td>60 ± 2</td>
<td>59 ± 3</td>
<td>66 ± 3</td>
<td>-</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>106 ± 2†</td>
<td>131 ± 2‡</td>
<td>118 ± 3†</td>
<td>108 ± 4†</td>
<td>1 vs. 3, 2 vs. 1,3, 4</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>68 ± 1†</td>
<td>73 ± 2‡</td>
<td>68 ± 3†</td>
<td>63 ± 3†</td>
<td>2 vs. 4</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>80 ± 1</td>
<td>93 ± 2</td>
<td>91 ± 3</td>
<td>78 ± 3</td>
<td>2 vs. 1,4, 3 vs. 1,4</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>38 ± 1</td>
<td>58 ± 2</td>
<td>50 ± 2</td>
<td>45 ± 3</td>
<td>1 vs. 3, 2 vs. 1,3, 4</td>
</tr>
<tr>
<td>MSNA burst frequency, bursts/minute</td>
<td>10 ± 1</td>
<td>14 ± 1</td>
<td>11 ± 2</td>
<td>10 ± 2</td>
<td>-</td>
</tr>
<tr>
<td>MSNA burst incidence, bursts/100 heartbeats</td>
<td>17 ± 2</td>
<td>22 ± 2</td>
<td>18 ± 3</td>
<td>15 ± 3</td>
<td>-</td>
</tr>
</tbody>
</table>
## Table S3 (continued). Comparison of Women by Institution.

<table>
<thead>
<tr>
<th>Demographic/Measurement</th>
<th>Institution 1 (n=12)</th>
<th>Institution 2 (n=33)</th>
<th>Institution 3 (n=8)</th>
<th>Institution 4 (n=0)</th>
<th>Significantly Different (p&lt;0.05) Pairwise Comparisons*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>22 ± 1</td>
<td>24 ± 1</td>
<td>29 ± 1</td>
<td>-</td>
<td>1 vs. 2,3</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23 ± 1</td>
<td>23 ± 1</td>
<td>22 ± 1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Heart rate, beats/minute</td>
<td>63 ± 2</td>
<td>61 ± 1</td>
<td>62 ± 3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>112 ± 4†</td>
<td>130 ± 2‡</td>
<td>122 ± 4†</td>
<td>-</td>
<td>1 vs. 2</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>73 ± 2†</td>
<td>71 ± 1‡</td>
<td>72 ± 3†</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>86 ± 3</td>
<td>91 ± 2</td>
<td>89 ± 3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>39 ± 3</td>
<td>58 ± 2</td>
<td>49 ± 3</td>
<td>-</td>
<td>2 vs. 1,3</td>
</tr>
<tr>
<td>MSNA burst frequency, bursts/minute</td>
<td>10 ± 2</td>
<td>10 ± 1</td>
<td>10 ± 2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MSNA burst incidence, bursts/100 heartbeats</td>
<td>16 ± 3</td>
<td>16 ± 2</td>
<td>17 ± 3</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Mean±SEM. MSNA, muscle sympathetic nerve activity. OC, oral contraceptive.

*Statistical analysis completed using the one-way analysis of variance (ANOVA) and Tukey post-hoc multiple comparison tests.

†Baseline blood pressure measured via brachial cuff.

‡Baseline blood pressure measured via brachial artery catheter.