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Sympathetic reactivity in young women with a family history of hypertension

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Greaney JL, Matthews EL, Wenner MM. Sympathetic reactivity in young women with a family history of hypertension. Am J Physiol Heart Circ Physiol 308: H816–H822, 2015. First published February 13, 2015; doi:10.1152/ajpheart.00867.2014.—Young adults with a family history of hypertension (+FH) have increased risk of developing hypertension. Furthermore, the blood pressure (BP) response to sympathoexcitatory stimuli in young adults can predict the future development of hypertension. Therefore, we hypothesized young women with a +FH would have exaggerated cardiovascular and sympathetic reactivity compared with young women without a family history of hypertension. Beat-by-beat mean arterial pressure (MAP) and muscle sympathetic nerve activity (MSNA) were measured in 14 women +FH (22 ± 1 yr, 21 ± 1 kg/m2, MAP 80 ± 2 mmHg) and 15 women −FH (22 ± 1 yr, 22 ± 1 kg/m2, MAP 78 ± 2 mmHg) during acute sympathoexcitatory maneuvers: cold pressor test, 2 min of isometric handgrip (HG) exercise at 30% of maximal voluntary contraction, and 3 min of postexercise ischemia (PEI; isolated activation of the skeletal muscle metaboreflex). During cold pressor test, the increase in BP was greater in women +FH (ΔMAP: +FH 16 ± 2 vs. −FH 11 ± 1 mmHg, P < 0.05), which was accompanied by an exaggerated increase in MSNA (ΔMSNA: +FH 17 ± 2 vs. −FH 8 ± 2 burst/min, P < 0.05). The increase in BP was greater in +FH during the last minute of HG (ΔMAP: +FH 23 ± 3 vs. −FH 12 ± 1 mmHg, P < 0.05) and during PEI (ΔMAP: +FH 17 ± 3 vs. −FH 9 ± 2 mmHg, P < 0.05). Similarly, the increase in MSNA was greater in +FH during both HG (ΔMSNA: +FH 12 ± 2 vs. −FH 6 ± 2 burst/min, P < 0.05) and PEI (ΔMSNA: +FH 16 ± 2 vs. −FH 4 ± 2 burst/min, P < 0.05). These data demonstrate that +FH women have greater BP and sympathetic reactivity compared with −FH women.

HEALTHY YOUNG ADULTS WITH A POSITIVE FAMILY HISTORY OF HYPERTENSION (+FH) have an increased risk of developing hypertension later in life (17, 24, 37, 39). The predictive strength of family history as a risk factor in the pathogenesis of hypertension is doubled for individuals with one hypertensive first degree relative and is nearly quadrupled with two such relatives (24). This is of particular importance for women’s health, because after menopause the prevalence of hypertension increases more in women: ~75% of women over the age of 60 yr are hypertensive (50a, 32, 46).

Aberrant neural control of the cardiovascular system plays a causal role in the development of hypertension (18, 33). Importantly, cardiovascular and sympathetic hyperreactivity to stress have emerged as predictors for the development of future hypertension (5, 7, 17, 27, 31, 37–39, 56), with an increased incidence of as much as ~23% in individuals exhibiting greater compared with less stress reactivity (9). A recent meta-analysis indicates that both greater reactivity to, and slower recovery from, a bout of mental stress predicts the future progression of cardiovascular disease risk status and further suggests the use of methods to manage stress responsivity in the prevention and treatment of cardiovascular disease (9). Furthermore, the physiological responses to laboratory stressors have been found to correspond to ambulatory measures of cardiovascular reactivity during activities of daily living (26). Young normotensive adults with exaggerated blood pressure (BP) reactivity to acute laboratory stressors have an increased incidence of future hypertension (37, 39, 50, 56). However, studies examining cardiovascular and sympathetic reactivity in young adults with a +FH have yielded conflicting results (30, 40, 42, 55). For instance, compared with young adults with no familial predisposition (−FH), young normotensive adults with a +FH demonstrated exaggerated increases in BP and muscle sympathetic nerve activity (MSNA) during mental stress (42), whereas the pressor and sympathetic responses to a cold pressor test (CPT) were blunted (30). It is important to note that the aforementioned studies were conducted primarily in young men, and, because of sex differences in the mechanisms underlying sympathetic regulation of the cardiovascular system (21), including differences in basal sympathetic outflow and the relation between total peripheral resistance and cardiac output, peripheral vascular adrenergic responsiveness (i.e., responsiveness of α- and β-adrenergic receptors), and vascular stiffness (8, 21–23, 47), the findings from these studies cannot be extrapolated to young women. To date, no studies have specifically examined sympathetic cardiovascular reactivity in healthy young women with a +FH. Therefore, examining potential dysregulation of sympathetic and cardiovascular function in normotensive young women with a +FH may provide novel mechanistic insight for this cohort’s predisposition to develop hypertension later in life.

Given the increased risk for young women with a +FH to develop hypertension later in life, coupled with the proposed predictive value of cardiovascular hyperreactivity, the purpose of the present study was to examine cardiovascular and sympathetic reactivity in young normotensive women with a +FH. We hypothesized that young women with a +FH would have exaggerated increases in BP and MSNA during acute labora-
ory sympathoexcitatory perturbations compared with young women with a −FH.

METHODS

Subjects. All experimental procedures and protocols were approved by the University of Delaware Institutional Review Board, and the study conformed to the standards outlined in the Declaration of Helsinki. Verbal and written consent were obtained voluntarily from all subjects before participation. Fourteen young women with a +FH (22 ± 1 yr) and fifteen women with a −FH (22 ± 1 yr) participated in this study. Using a standard clinical medical history form from the Nurse Managed Health Center at the University of Delaware, young women self-identified as to whether their father or mother have been diagnosed with high BP; a positive response for either (or both) parents was subsequently used to determine family history status. Women with a −FH indicated that neither parent has high BP and comprised the control group. All subjects were normotensive (resting systolic BP < 120 mmHg and diastolic BP < 80 mmHg), nondiabetic, and not taking over-the-counter or prescription medications or supplements with primary or secondary cardiovascular effects (e.g., statins, antihypertensives, antidepressants, etc.). Nine +FH and seven −FH women indicated on the medical history form that they performed aerobic exercise (running, biking, swimming) 3–5 days/wk. Subjects were nonobese (body mass index < 30 kg/m²) and did not use tobacco products. Body fat percent was determined using the Tanita scale. Young women were tested either during the early morning or late afternoon and had abstained from alcohol, caffeine, and strenuous physical activity for the preceding 24 h. Heart rate was monitored using a lead II electrocardiogram (Dinamap Dash 2000; GE Medical Systems, Milwaukee, WI). Beat-by-beat arterial BP was measured noninvasively by a servo-controlled finger photoplethysmograph (Finometer; Finapres Medical Systems, Amsterdam, the Netherlands) placed on the middle finger of the nondominant hand. Automated brachial artery BPs (Dinamap Dash 2000; GE Medical Systems) verified absolute Finometer-derived BP measurements. Respiratory movements were monitored using a strain-gauge pneumograph (Pneumotrace; UFI, Morro Bay, CA) placed in a stable position over the abdomen and were used to ensure that subjects did not inadvertently perform Valsalva maneuvers or breath holds during the protocol.

Multiunit postganglionic MSNA was recorded using standard microneurographic techniques, as previously described in detail (19, 51, 54). Briefly, these recordings were obtained by inserting unipolar tungsten microelectrodes percutaneously through the intact, unanesthesitized skin and positioning the electrode into muscle nerve fascicles of the peroneal nerve near the fibular head. A reference microelectrode was inserted 3 cm away. Neural signals were amplified (70,000-fold), band-pass filtered (700–2,000 Hz), rectified, and integrated (0.1-s time constant) to obtain mean voltage neurograms (Nerve Trafiic Analyzer, model 662c-3; University of Iowa Bioengineering, Iowa City, IA). MSNA recordings were identified and verified by the presence of spontaneously occurring bursts with characteristic pulse synchronicity, responsiveness to an exo-dyapnoic breath hold or Valsalva maneuver, and lack of response to arousal stimuli or skin stimulation.

Experimental protocol. Three common sympathoexcitatory maneuvers were used to investigate cardiovascular and sympathetic reactivity in women +FH and −FH: the CPT, isometric handgrip (HG), and postexercise ischemia (PEI), as these perturbations elicit robust and reproducible increases in BP and MSNA (41, 52) and are commonly used in laboratory settings to assess sympathetic cardiovascular reactivity (30, 37, 57). Women were tested in the supine position; laboratory temperature was maintained between 20 and 22°C. The maximal voluntary contraction (MVC) of the dominant hand was tested by having subjects squeeze a commercially available device (ADInstruments, Bella Vista, NSW, Australia) at maximal effort three to five times. The highest force production was subsequently used as the MVC, which was then used to calculate the relative work rate of 30% for the experimental protocol. After subject instrumentation and a satisfactory MSNA recording were obtained, subjects rested quietly for 10 min.

Continuous measures of BP and MSNA were made throughout the experimental protocol. Resting baseline data collection preceded the CPT and HG. For the CPT, the subject’s dominant hand was placed in an ice bath for 2 min. Adequate nerve recordings were obtained in seven women with a +FH and eight women with a −FH during the CPT. For HG and PEI, women performed isometric exercise at 30% of their MVC for 2 min. Women were provided with visual feedback of force production during HG. Force production was recorded to compare the exercise stimulus between groups. During HG, ratings of perceived exertion were obtained using the standard 6–20 Borg scale (3). With 5 s remaining in HG, an occlusion cuff placed on the upper arm of the exercising limb was rapidly inflated to suprasystolic BP (≥250 mmHg). The occlusion cuff remained inflated for 3 min and 15 s following the completion of exercise (i.e., PEI). PEI was used to isolate activation of the skeletal muscle metaboreflex (1, 19, 35), as this is one of the primary mechanisms contributing to sympathetic activation during isometric exercise (35). The additional 15 s of PEI were incorporated to account for the robust and transient initial decrease in BP and MSNA that occurs when exercise is immediately stopped. During the HG/PEI trial, successful nerve recordings were obtained in 8 women with a +FH and 10 women with a −FH. The CPT and HG/PEI were separated by at least 15 min to allow BP and MSNA to return to baseline. Brachial BP was used to confirm that BP had returned to resting values before the start of the second perturbation.

Data analysis. All data were recorded at 1,000 Hz (Powerlab and Chart, ADInstruments). MSNA bursts were identified from the mean voltage neurogram using a customized LabVIEW program with fixed criteria (15, 16), which generated an synchronous burst-by-burst data file of all recorded variables accounting for the latency from the R wave of the electrocardiogram (14) and incorporated a signal-to-noise ratio of at least 3:1. The MSNA signal was calibrated by assigning the voltage of the average of the three largest bursts during baseline the value of 100 arbitrary units and, all other bursts within a trial were normalized with respect to this value. MSNA was quantified as burst frequency (bursts/min) and burst incidence (bursts/100 heartbeats), which have been demonstrated to be reproducible within a subject over time and comparable between groups (29).

Cardiovascular and sympathetic variables were calculated as mean values over an initial 5-min resting baseline. Because we were primarily interested in differences in “reactivity” between groups, we examined the time period of the greatest response for each perturbation. For the CPT, data were analyzed during 2 min of baseline before the subject placed her hand in cold water, and during each minute of the CPT (1-min averages). Because the peak cardiovascular and sympathetic responses to a CPT occur in the second minute (41, 52), this time period of peak responsiveness (i.e., the second minute) was used for all group comparisons. For the HG/PEI trial, sympathetic and cardiovascular variables were calculated as mean values during the 5-min baseline preceding HG, during the peak responsiveness to HG (the last minute), and during the full 3 min of PEI (excluding the initial 15 s). Because no significant changes in BP or MSNA occur during the ischemic period (52), the entire PEI was used for group comparisons.

Statistical analysis. Subject characteristics were compared using unpaired t-tests (SPSS 19.0). Comparisons of cardiovascular and

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sympathetic variables for the CPT were conducted using unpaired t-tests, and a two-way repeated-measures ANOVA was used to compare differences during HG/PEI. Results are reported as means ± SE, and the α-level was set at P < 0.05.

RESULTS

Subject characteristics are presented in Table 1. The groups were well-matched for age, anthropometric characteristics, resting BP, and resting MSNA (P > 0.05 for all).

Cardiovascular and sympathetic reactivity to the CPT. Original recordings of BP and MSNA during the CPT in one young woman with a +FH and one young woman with a −FH are presented in Fig. 1. The CPT elicited robust increases in BP, MSNA, and heart rate in both groups (Fig. 2 and Table 2). The increase in mean arterial pressure during the CPT was greater in young women with a +FH compared with those with a −FH (Table 2). The increases in heart rate were not different between groups (Table 2).

Cardiovascular and sympathetic reactivity to HG and PEI. As expected, isometric HG elicited increases in BP, MSNA, and heart rate in each group (Fig. 3 and Table 2). In young women with a +FH, isometric HG elicited greater increases in MAP compared with women with a −FH (Fig. 3A and Table 2; P < 0.05). Similarly, the increases in MSNA during HG were greater in young women with a +FH (Fig. 3, B and C; P < 0.05). There were no group differences in the heart rate response to static HG (Table 2). MVC (−FH 229 ± 26 vs. +FH 250 ± 19 N; P = 0.54), as well as force production during HG (−FH 65 ± 7 vs. +FH 71 ± 5 N; P = 0.52), were not different between groups. All subjects were able to maintain the target force production during HG (30% MVC). In addition, reported ratings of perceived exertion during isometric HG were not different between subject groups (−FH 13 ± 1 vs. +FH 13 ± 1 Borg units; P > 0.05).

During PEI, MAP and MSNA remained elevated compared with baseline in both subject groups. The increase in MAP during PEI was greater in young women with a +FH (Fig. 3D and Table 2; P < 0.05). In addition, young women with a +FH exhibited greater increases in MSNA during PEI compared with young women with a −FH (Fig. 3, E and F; P < 0.05). As expected, heart rate returned to baseline during PEI, and this response was not different between subject groups (Table 2).

DISCUSSION

The novel finding of the present investigation was that BP and sympathetic reactivity were exaggerated in young normo-

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Table 1. Subject characteristics

<table>
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Values are means ± SE. +FH and −FH, with or without a family history of hypertension, respectively; BMI, body mass index; BP, blood pressure; MSNA, muscle sympathetic nerve activity.

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Our data demonstrate greater increases in systolic BP, diastolic BP, and MAP, along with MSNA, in young women with a familial predisposition for hypertension during multiple acute laboratory stressors: CPT, isometric HG, and PEI. Taken together, a greater sympathetic cardiovascular reactivity may contribute to the increased risk for the future development of hypertension in young women with a +FH. These findings have important clinical implications in potentially helping to explain the emerging link between sympathetic cardiovascular hyperreactivity to stress and cardiovascular disease.

Large-scale longitudinal studies indicate that exaggerated cardiovascular reactivity to a CPT is linked to an increased incidence of future hypertension (49, 50, 56), demonstrating the predictive clinical utility of the CPT. In the present investigation, young women with a +FH, who are already at an elevated risk for developing hypertension (17, 24, 37, 39), demonstrated greater increases in BP during the CPT compared with young women with a −FH. Importantly, a CPT-induced increase in systolic BP of 20 mmHg is associated with an approximately twofold increase in the risk of hypertension after adjusting for cardiovascular risk factors and closely approximates the increased risk observed for a similar increase in basal systolic BP (39). In the present study, young normotensive women with a +FH displayed an average increase in systolic BP of 19 mmHg during the CPT, compared with women with a −FH who displayed an average increase in systolic BP of 13 mmHg (Table 2). This augmented pressor response was accompanied by greater increases in MSNA, indicating that exaggerated cardiovascular reactivity in women with a +FH is likely mediated, at least in part, by the sympathetic nervous system. Lambert and Schlaich (30) report an increase of 17 mmHg in systolic BP during a CPT in young adults (men and women) with +FH (n = 14), which is consistent with the increases noted in the present study (19 mmHg). Interestingly, in the aforementioned study (30), the increases in systolic BP during a CPT in adults with a +FH were blunted compared with the responses in adults with a −FH (33 mmHg, n = 11) or adults with diagnosed hypertension (22 mmHg, n = 8). In contrast, we report herein that the increases in systolic BP during a CPT in women with a +FH are greater than those in women without. The reason(s) for these differing study conclusions remain unclear; however, they likely reflect the variability of responses in the control groups of each study, as well as the inclusion of both sexes in the earlier study (30). The increases reported in the control group of our study (−FH) appear generally consistent with typical increases in systolic BP during a CPT previously reported in young healthy women, although the existence of familial history of hypertension was not specified in those women (25).

The sympathetic nervous system plays an important role in the pathogenesis of essential hypertension (18, 33). Cross-sectional studies have demonstrated that borderline hypertensive adults have elevated sympathetic nervous system activity at rest compared with normotensive subjects (11, 44). Furthermore, sympathetic hyperreactivity to stress has emerged as an independent predictor of the development of future hypertension in men (aged 19 yr at entry and 37 yr at follow-up) (17). Despite similarities in MSNA at rest between groups in the present study, the extent to which MSNA increased during multiple stressors/perturbations was greater in women with a +FH. Therefore, the results of the present study demonstrate that altered sympathetic reactivity may represent a potential novel mechanism contributing to the increased risk for developing hypertension in young women with a +FH.

In addition to demonstrating augmented pressor and sympathetic responses to the CPT, young women with a +FH also exhibited greater increases in BP and MSNA during isometric HG and PEI, a technique used to isolate activation of the muscle metaboreflex (1, 12). The magnitude of the increase in MAP during moderate HG in the young women with a +FH in the present study is consistent with the increases of ~25–30 mmHg reported in young men with a +FH (n = 13) during static HG to exhaustion performed at 30% MVC (55). Impor-
tantly, skeletal muscle metaboreflex function, one of the mechanisms mediating the neuro-cardiovascular responses to exercise, is altered in adults with elevated resting BP (12, 19), contributing to the greater increases in BP and MSNA during isometric HG in hypertensive adults compared with their healthy counterparts (2, 12, 20, 28, 36). Therefore, the results of the present study likewise suggest that the potentiated pressor and sympathetic responses to isometric exercise in young women with a +FH may be mediated, at least in part, by an exaggerated skeletal muscle metaboreflex. Although outside the scope of the present investigation, this represents an important future line of inquiry.

The advantage of physiological reactivity stress testing in an acute laboratory setting is that sophisticated measures of cardiovascular function can be performed under standardized conditions, during which confounding factors can be eliminated and stimuli can be manipulated experimentally. Although few attempts to generalize cardiovascular reactivity assessed in acute laboratory settings to the “real world” remain a limitation of the cardiovascular reactivity hypothesis, the use of data “aggregation” across multiple stressors can improve generalizability (48). The aggregation across various stressors in the present study (CPT, HG, and PEI), therefore, lends further support to our conclusion that young women with a +FH exhibit heightened cardiovascular and sympathetic reactivity to acute stress. Future longitudinal follow-up studies of these women are clinically relevant and important to establish a direct link between stress reactivity and the development of cardiovascular disease in this cohort of young healthy women.

Although our data demonstrate a role for sympathetic hyperreactivity in mediating the exaggerated BP responses observed in women with a +FH, other mechanisms may also contribute, such as structural or functional changes in the peripheral vasculature. Vascular dysfunction, evidenced by impaired endothelium-dependent dilation and increased aortic stiffness, is evident in the offspring of hypertensive parents compared with offspring of nonhypertensive parents (10, 13). In addition, young adults with a hypertensive familial predisposition also have higher resting plasma concentrations of norepinephrine and endothelin-1 (10). We speculate that sympathetically mediated repeated increases in BP during stress may directly affect the peripheral vasculature via arteriolar remodeling (34) and increases in blood viscosity (45), both of which increase total peripheral resistance. In addition, increased arterial stiffness, assessed via pulse wave velocity, is greater in young adults with a high familial risk of hypertension (10) and, therefore, may also contribute to the augmented reactivity in women with a +FH in this study. Therefore, alterations in vascular function and stiffness and subsequent subclinical atherosclerosis, and their implications for the future progression to hypertension later in life, may also contribute to exaggerated cardiovascular reactivity in young women with a +FH. Future studies prospectively examining potential alterations in vasoconstrictor signaling mechanisms are clinically important.

**Limitations.** All women were classified based on self-report using a clinical medical history form, and we did not obtain medical records of the parents. Unfortunately, we do not have...
additional information regarding the parental hypertension diagnosis (e.g., primary or secondary) or the parental medical records, including details regarding specific BP values, medication use, or age of diagnosis. As such, a misclassification of young women may jeopardize interpretation of the results. Despite our reliance on “self-report” of a parental hypertension to define the two subject groups in this study, we observed robust differences in BP and sympathetic reactivity during various stressors between subject groups. Future studies using stricter and more detailed parental medical histories are needed to confirm our findings. Interestingly, the predictive strength of family history as a risk factor for the development of hypertension doubles when having two hypertensive parents (24), and young men with two hypertensive parents have a 20-fold increase in the likelihood of developing hypertension compared with young men with only one hypertensive parent (53).

In the present study, only one young woman self-identified as having two parents with hypertension, thus precluding a meaningful physiological comparison between young women with one vs. two parents with high BP. Given the significant increase in cardiovascular risk posed by having two parents with hypertension, future studies investigating BP and sympathetic reactivity in such women are clinically relevant and necessary to more fully characterize the future cardiovascular implications of familial hypertension.

In addition, because we only studied women, we cannot extend our findings to men or make meaningful sex comparisons. Future investigations are warranted to determine potential sex differences in reactivity between young men and women with a +FH. Finally, we acknowledge that our results are limited to an acute laboratory setting, and longitudinal follow-up studies are required to establish a direct link to the future development of hypertension in women. Despite these limitations, clear group differences were observed in response to multiple cardiovascular stressors in the present study. Thus these findings represent an important first step in elucidating the potential mechanisms underlying the increased risk for the development of hypertension in young women with a +FH.

**Perspectives.** Our novel findings demonstrate that normotensive young women with a +FH demonstrate exaggerated BP and sympathetic reactivity during acute laboratory stressors. Physiologic responses to laboratory stressors have been found to correspond to ambulatory measures of cardiovascular reactivity during activities of daily living (26). Current guidelines recommended 5 min of seated rest before taking BP measurements (43); because BP reactivity is a strong predictor of the risk of future hypertension (37, 39, 50, 56), it may be advantageous to also clinically assess the pressor response to acute stressors. The results of the present study suggest that cardiovascular reactivity in response to stress may be an important predictor of future cardiovascular disease risk in young, otherwise healthy, women with a +FH.

Large-scale longitudinal follow-up studies examining the clinical utility of sympathetic cardiovascular reactivity in predicting hypertensive disorders in women (preeclampsia, gestational hypertension, or postmenopausal hypertension) are necessary.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**


**REFERENCES**

BLOOD PRESSURE AND SYMPATHETIC REACTIVITY IN WOMEN


