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ABSTRACT

A positive family history of hypertension (+FH) is a risk factor for the future development of hypertension. Hypertension is associated with reductions in baroreflex sensitivity (BRS). Therefore, we hypothesized that young women with a +FH (n=12, 22±1 yrs, BMI 21±1 kg/m^2, MAP 79±1 mmHg) would have lower BRS compared to young women without a family history of hypertension (-FH) (n=13, 22±1 yrs, BMI 21±1 kg/m^2, MAP 77±2 mmHg, all P>0.05 between groups). Continuous measurements of muscle sympathetic nerve activity (MSNA), blood pressure, and electrocardiogram derived R-R interval were recorded at rest and during a Valsalva maneuver. Both cardiovagal and vascular sympathetic BRS were assessed. Resting cardiovagal BRS was reduced in the +FH women (all sequences: -FH 32.3±3.7 vs. +FH 20.2±2.9 ms/mmHg, P = 0.02). Cardiovagal BRS during phase IV (-FH 16.5±2.7 vs. +FH 7.6±1.3 ms/mmHg, P < 0.01) but not phase II (-FH 5.5±0.9 vs. +FH 5.0±0.8 ms/mmHg, P = 0.67) of the Valsalva maneuver was also lower in the +FH women. Vascular sympathetic BRS at rest (-FH -2.38±0.7 vs. +FH -2.33±0.3 bursts/min/mmHg, P = 0.58) and during the Valsalva (-FH -0.74±0.23 vs. +FH -0.66±0.18 bursts/15s/mmHg, P = 0.79) were not different between groups. These data suggest that healthy young women with a positive family history of hypertension have reduced cardiovagal BRS. This may be one mechanism contributing to the increased incidence of hypertension in this population later in life.

New and Noteworthy

Having a family history of hypertension increases the risk of developing future hypertension. Reductions in baroreflex function have been demonstrated in hypertension, and are an important marker for future cardiovascular disease. We show that young women with a family history of hypertension have lower cardiovagal baroreflex sensitivity. This alteration in autonomic function may be one mechanism contributing to the future incidence of hypertension in this patient population.

INTRODUCTION

Cardiovascular disease is the leading cause of death in women, with hypertension being the most prevalent cardiovascular disorder (Hopkins and Hunt 2003; Mozaffarian et al. 2015). Having a positive family history of hypertension (+FH) greatly increases the risk for developing the disease (Flaa et al. 2008; Hunt et al. 1986; Matthews et al. 2004; Menkes et al. 1989). In fact, the risk of developing hypertension is approximately doubled for each first degree relative with diagnosed hypertension (Hunt et al. 1986). This association is especially important for women's health since postmenopausal women have a greater prevalence of hypertension compared to men (Lima et al. 2012; Mozaffarian et al. 2015; Yanes and Reckelhoff 2011).

The baroreflex plays a critical role in the regulation and maintenance of blood pressure (BP). It has been well established that adults with hypertension have impaired baroreflex function (Bristow et al. 1969; Laterza et al. 2007), and as such, autonomic dysregulation has been postulated as a key mechanism in the etiology of hypertension. To this end, normotensive adults at risk of developing future hypertension because of a positive family history of hypertension (+FH) also show alterations in baroreflex function; however, these data were done solely in men (Boutcher et al. 2009; Parmer et al. 1992). Of these studies, Parmer et al. (Parmer et al. 1992) found reduced baroreflex sensitivity (BRS), and Boutcher et al. (Boutcher et al. 2009) found reduced carotid BRS but no differences in cardiopulmonary BRS. Several studies have demonstrated sex differences in BP control and baroreflex function (Charkoudian et al. 2005; Dutoit et al. 2010; Fu et al. 2009; Hart et al. 2011; Hart et al. 2009). Therefore, it is important to examine the impact of a +FH on autonomic function in women since decreased BRS may increase the risk of future hypertension and cardiovascular events.

Despite women having the greater prevalence of developing hypertension later in life, to date, studies have not investigated BRS in young women with +FH. Therefore, the purpose of the present study was to examine BRS in young normotensive women with a +FH. We hypothesized that young women with a +FH would have a decreased cardiovagal and vascular sympathetic BRS compared to young women without a family history of hypertension (-FH).

METHODS

Subjects

Twenty-five healthy young women completed for this study: 13 women -FH (22±1 yrs) and 12 women +FH (22±0.3 yrs). Positive family history of hypertension was defined as either the subject's mother or father having been diagnosed with hypertension. Women self-reported their family history using a standard medical history questionnaire from the University of Delaware's Nurse Managed Primary Care Center. Five women in each group participated in our previous study (Greaney et al. 2015; Matthews et al. 2017). All subjects were normotensive (resting systolic BP < 120 mmHg and diastolic BP < 80 mmHg), non-obese (BMI < 30 kg/m^2), non-smokers, and free from any known cardiovascular or chronic diseases. Subjects were not taking any over-the-counter or prescription medications or supplements with primary or secondary cardiovascular effects, such as antihypertensives, statins, or antidepressants. If subjects were taking an oral contraceptive, they were tested during the placebo phase of their regimen (-FH n=9; +FH n=7). Otherwise, subjects were tested during the early follicular phase of their menstrual cycle (-FH n=4; +FH n=5). All subjects were familiarized with the equipment and experimental protocol before the testing visit. All experimental procedures were approved by the University of Delaware Institutional Review Board and all women gave verbal and written

consent prior to study participation. All study related activities conformed to the standards outlined in the Declaration of Helsinki.

Experimental Measurements

Subjects were instructed to report to the laboratory on the day of testing after fasting for at least four hours and abstaining from alcohol, caffeine, and strenuous exercise for at least 24 hours. During testing procedures, heart rate was monitored using a single-lead electrocardiogram (ECG; Dinamap Dash 2000; GE Medical Systems, Milwaukee, WI, USA) and was used to calculate R-R intervals. Beat-by-beat arterial BP was measured using a Finometer (Finapres Medical Systems, Amsterdam, Netherlands), which was placed on the middle finger of the subject's non-dominant hand and calibrated using the manufacturer's instructions. The Finometer is a reliable and noninvasive technique to track arterial BP both at rest and during autonomic cardiovascular testing (Imholz et al. 1990; Imholz et al. 1988; Imholz et al. 1998). Automated brachial artery BP was also measured (Dinamap Dash 2000; GE Medical Systems, Milwaukee, WI, USA) and used to verify the absolute Finomoter-derived BP measurements. Respiratory rate was monitored using a strain-gauge pneumograph (Pneumotrace; UFI, Morro Bay, CA, USA) placed in a stable position around the upper abdomen.

Multiunit postganglionic muscle sympathetic nerve activity (MSNA) was measured via peroneal microneurography, as previously described (Greaney et al. 2015; Vallbo et al. 1979; Vallbo et al. 2004; Wenner et al. 2007). Briefly, nerve recordings were obtained using a standard unipolar tungsten microelectrode inserted into the peroneal nerve close to the fibular head, while a reference microelectrode was inserted approximately 3 cm away on the lower leg. The nerve signals were amplified (70,000-fold), bandpass filtered (700-2,000 Hz), rectified, and integrated (time constant: 0.1 s) using a nerve traffic analyzer (model 662c-4; University of Iowa

Bioengineering, Iowa City, IA, USA). Nerve bursts were determined to be the result of MSNA and not skin sympathetic nerve activity if electrical stimulation with the microelectrode caused a visible muscle twitch, light stroking of the skin did not elicit nerve bursts, passive stretch of the leg resulted in afferent nerve bursts, and there was an increase in burst activity in response to an end-expiratory breath hold. In accordance with recent guidelines (Hart et al. 2017; Shoemaker et al. 2018; White et al. 2015), only bursts with a >3:1 signal-to-noise ratio that were pulse synchronous were accepted for analysis.

Experimental Protocol

Cardiovagal and vascular sympathetic BRS were assessed during ten minutes of rest and during a Valsalva maneuver. To perform the Valsalva maneuver, subjects were asked to expire into a mouthpiece maintaining a pressure of 40 mmHg, or best effort, for 15 s. During the Valsalva maneuver, intrathoracic and intra-abdominal pressure increases causing a brief rise in peripheral BP (phase I), followed by a prolonged decrease in BP (phase II). Immediately following the cessation of the Valsalva maneuver a brief drop in BP occurs (phase III) followed by a sustained increase in BP (phase IV). The slope of the relation between systolic BP (SBP) and R-R interval during the two prolonged phases of the Valsalva maneuver (phases II and IV) were examined to assess cardiovagal BRS (Farquhar et al. 2000; Wenner et al. 2006). Only regressions with an r^2 value of $\geq$0.7 were included in the analysis (Farquhar et al. 2000; Wenner et al. 2006). During the Valsalva maneuver, we examined the total number of bursts that occurred during exhalation to the change in diastolic BP (DBP) as an index of vascular sympathetic BRS as previously described (Cox et al. 2002; Delaney et al. 2010; Fu et al. 2009; Fu et al. 2005). The number of bursts during the 15 seconds of expiration was related to the maximal change in DBP (calculated from the highest DBP at the initiation of straining to the

minimum DBP during the maneuver) (Cox et al. 2002; Delaney et al. 2010; Fu et al. 2009; Fu et al. 2005).

Data Analysis

Resting cardiovagal BRS was assessed during baseline using the sequence method and HemoLab software (Harald Stauss Scientific, Iowa City, IA, USA). R-to-R intervals were regressed over SBP for each sequence of four or more consecutive cardiac cycles where both variables increased (up sequences) or decreased (down sequences) in unison. A minimum acceptable r value of 0.8 for each sequence was required for inclusion into the calculation of cardiovagal BRS. The average regression slope for up, down, and combined (up and down together) sequences was calculated and used to characterize cardiovagal BRS at rest. Resting vascular sympathetic BRS was determined by examining the spontaneous fluctuations in DBP and MSNA. MSNA bursts were binned in 3 mmHg bins using custom Labview software (Fairfax et al. 2013). The regression line was weighted to account for the number of cardiac cycles within each bin. Bins without MSNA activity (zeros) were included in the analysis. A minimum acceptable r value of 0.5 was used as an inclusion criterion (Wenner et al. 2007). The slope of the relationship between DBP and MSNA was used as an index of vascular sympathetic BRS, or gain around the operating point.

Heart rate variability (HRV) analysis was also performed to further assess resting autonomic function. Heart rate variability is largely dependent on modulation of vagal activity (1996) and is therefore an index of parasympathetic tone. R-R intervals were analyzed with Kubios HRV software (Tarvainen et al. 2014) (University of Eastern Finland, Joensuu, Finland). The time domain and frequency domain using the fast Fourier transformation were used to assess HRV. Frequency power was categorized as low frequency bands (LF; 0.04-0.15 Hz) and high

frequency bands (HF; 0.15-0.4 Hz). The very low frequency band (<0.04 Hz) was not analyzed due to short recording time.

Statistical Analysis

Participant characteristics and baroreflex function were compared between +FH and –FH groups using unpaired t-tests. Results are reported as means ± SE. The alpha level for significance was set at $P<0.05$.

RESULTS

Subject characteristics are presented in Table 1. The two groups were well-matched for age, BMI, and resting BP (all $P > 0.05$). MSNA was obtained in a subset of women (-FH n=8; +FH n=8). Resting burst frequency (-FH 8±2 vs. +FH 9±1 bursts/min, $P = 0.90$) and burst incidence (-FH 14±3 vs. +FH 13±1 bursts/100 heart beats, $P = 0.61$) were not different between groups.

Baroreflex Sensitivity

Resting cardiovagal BRS was assessed using the sequence method. The +FH group had lower resting cardiovagal BRS for up sequences (-FH 30.6±4.1 vs. +FH 18.1±2.7 ms/mmHg, $P = 0.02$) and combined up and down sequences (-FH 32.3±3.7 vs. +FH 20.2±2.9 ms/mmHg, $P = 0.02$). There was also a trend towards lower cardiovagal BRS for down sequences (-FH 33.1±4.4 vs. +FH 22.9±3.5 ms/mmHg, $P = 0.09$). Both groups had a similar number of cardiac cycles (-FH 509±47 vs. +FH 519±60, $P = 0.90$) during the recording period.

Cardiovagal BRS during the Valsalva maneuver is presented in Figures 1 and 2. As shown in Figure 1, cardiovagal BRS was lower in +FH women during phase IV of the Valsalva maneuver (-FH 16.5±2.7 vs. +FH 7.6±1.3 ms/mmHg, $P < 0.01$). During phase II of the Valsalva

maneuver (Figure 2), there were no differences in cardiovagal BRS between groups (-FH 5.5±0.8 vs. +FH 5.0±0.6 ms/mmHg, $P = 0.67$). Mean pressure achieved during exhalation was similar between groups (-FH 33±3 vs. +FH 31±3 mmHg, $P > 0.05$).

Vascular sympathetic BRS was determined in a subset of women in whom we obtained nerve recordings (-FH n=8; +FH n=8). Resting sympathetic BRS (-FH -2.38±0.7 vs. +FH -2.33±0.3 burst/min/mmHg, $P = 0.58$) was not different between groups. During the Valsalva maneuver, the decline in DBP (-FH Δ-20±4 vs. +FH Δ-20±4 mmHg, $P = 0.82$) was similar between groups. Valsalva-derived vascular sympathetic BRS is presented in Figure 3. There were no differences in vascular sympathetic BRS between groups (-FH -0.74±0.23 vs. +FH -0.66±0.18 burst/min/mmHg, $P = 0.79$).

Heart Rate Variability

HRV analysis was performed to further assess autonomic function at rest with an emphasis on HRV indices of parasympathetic function. Heart rate during the recording period tended to be lower in the –FH group (-FH 62±1 vs. +FH 69±3 beats/min, $P = 0.05$), whereas R-R interval tended to be higher (-FH 977±18 vs. +FH 899±44 ms, $P = 0.11$). The –FH group had higher pNN50 (-FH 46.8±5.2 vs. +FH 26.3±6.2 %, $P = 0.02$). All other time domain HRV indices (SDNN: -FH 84±10 vs. +FH 75±13 ms, $P = 0.59$; RMSSD: -FH 85±13 vs. +FH 73±20 ms, $P = 0.61$), and all frequency domain HRV indices (HF: -FH 3552±1276 vs. +FH 1260±270 ms^2, $P = 0.10$; LF: -FH 2274±694 vs. +FH 1173±280 ms^2, $P = 0.17$; total power: -FH 7321±2058 vs. +FH 5880±1661 ms^2, $P = 0.59$; LF/HF ratio: -FH 0.83±0.16 vs. +FH 1.16±0.26, $P = 0.28$) were not different between groups.

DISCUSSION

The main novel finding of the current study is that healthy young, normotensive women with a +FH have reduced cardiovagal BRS compared to women with a –FH. This was demonstrated using two distinct measures of BRS (resting spontaneous BRS and Valsalva-derived BRS). This is important because suppressed baroreflex function is associated with established hypertension (Bristow et al. 1969; Laterza et al. 2007), and having a +FH increases the risk of developing hypertension (Hunt et al. 1986). Furthermore, low cardiovagal BRS has been proposed as a meaningful variable for risk stratification (Kiviniemi et al. 2014) (La Rovere 2000). Our data suggest that young normotensive women at risk for future hypertension display alterations in autonomic function. Thus, these data are especially important for women's health given the greater prevalence of hypertension in postmenopausal women (Lima et al. 2012; Mozaffarian et al. 2015; Yanes and Reckelhoff 2011).

Impaired BRS has been demonstrated in young men with a +FH, but to our knowledge, no studies have examined women. Parmer et al. (Parmer et al. 1992) found reduced cardiovagal BRS in response to both bolus phenylephrine administration and amyl nitrite inhalation in both normotensive and hypertensive men with a family history of hypertension. Boutcher et al. (Boutcher et al. 2009) used lower body negative pressure to challenge the baroreflex and found decreased carotid BRS but no differences in cardiopulmonary BRS between +FH and –FH men. We examined baroreflex function using the spontaneous technique at rest, as well as during the Valsalva maneuver. Importantly, our findings of reduced cardiovagal BRS at rest and during the Valsalva maneuver in +FH women are consistent with those studies in men utilizing vasoactive drugs (Parmer et al. 1992) or neck suction (Boutcher et al. 2009), which can elicit larger changes in blood pressure. Therefore, our data extends previous findings to show that women with a +FH also display lower cardiovagal BRS. This autonomic dysregulation may contribute to the

development of hypertension in these otherwise healthy individuals. Although data have shown this reduction in cardiovagal BRS sensitivity before in men, to our knowledge, this is the first manuscript to show this also occurs in women and is an important extension of prior work. Demonstrating these findings in women is important given the increased rates of hypertension during pregnancy as well as after menopause; additional longitudinal data are needed to understand the association between altered autonomic function in women with a family history of hypertension and the risk of preeclampsia and hypertension later in life.

The current investigation did not observe differences in vascular sympathetic BRS (during rest or the Valsalva). However, it is possible that in such a young cohort (22±1 yrs) differences are masked, and older women need to be studied to determine if having +FH impacts vascular sympathetic baroreflex sensitivity. Although resting muscle sympathetic nerve activity increases with age (Ng et al. 1993), aging does not appear to effect vascular sympathetic baroreflex sensitivity in healthy men (Davy et al. 1998; Ebert et al. 1992; Tanaka et al. 1999). However, older women have lower vascular sympathetic baroreflex sensitivity compared to older men (Okada et al. 2012). Given that impaired baroreflex sensitivity may contribute to hypertension along with the known sex differences in hypertension in older adults, we speculate that vascular sympathetic baroreflex sensitivity may be reduced in women as they become older, potentially more so in those with a family history of hypertension. Indeed, estrogen replacement enhanced vascular sympathetic (but not cardiovagal) baroreflex sensitivity in postmenopausal women (Hunt et al. 2001). Thus, future studies are needed to extend the current findings to older women.

Contrary to vascular sympathetic baroreflex sensitivity, cardiovagal BRS decreases with age (Rudas et al. 1999) and is also reduced in hypertension (Bristow et al. 1969; Laterza et al.

2007). The modified Oxford technique is considered the 'gold standard' for assessing baroreflex function, however it has recently been shown that BRS derived from Phase IV of the Valsalva maneuver was a significant predictor of cardiovascular mortality in middle-aged adults (Kiviniemi et al. 2014). Taken together with the baroreflex data in aging and hypertension, this may suggest that cardiovagal BRS is a more sensitive assessment of autonomic function and predictor of cardiovascular disease. Given this altered BRS in both men (Parmer et al. 1992) and women (current study) with a +FH, coupled with the important prognostic value of cardiovagal BRS (Kiviniemi et al. 2014), we speculate that low cardiovagal BRS may be an early marker of future disease in those at risk for developing hypertension. The impaired BRS may also help to explain the aberrant BP and sympathetic reactivity previously found in adults with a +FH (Fonkoue et al. 2016; Greaney et al. 2015; Matthews et al. 2017). Future longitudinal research in young adults with a +FH is warranted.

Given that HF power is a strong indicator of parasympathetic tone, we would anticipate this variable to be different between groups. Although the HF component of HRV did not reach statistical significance, we observed a trend toward a lower HF power in +FH women (P=0.10), which was almost 3 times lower than in women without a family history of hypertension. However, a large inter-individual variation between HRV and vagal tone has been reported (Draghici and Taylor 2016), and it has been suggested that HRV and baroreflex sensitivity have independent predictive value. Specifically, HRV is reflective of tonic vagal tone whereas baroreflex sensitivity is reflex vagal activity (Hoffmann et al. 2000). Furthermore, these variables have been weakly correlated, suggesting complexity within this relationship (Hoffmann et al. 2000). The lack of statistical differences in RR-interval between groups may also explain why indices of HRV were not different. Given that HR tended to be higher in the +FH women,

one would anticipate a lower RR interval. However, HR and RR-interval are not linearly related (Draghici and Taylor 2016), and given that RR-interval generally has a much larger standard deviation within resting ranges (Stauss 2014), it may not be surprising that the statistical results of the two do not mirror one another (Draghici and Taylor 2016).

We recognize there are several limitations with the current investigation. We relied on self-reported parental history of hypertension, and this may have caused some misclassification of subjects. Regardless, the robust between-group differences were still evident. We also did not collect blood samples to measure norepinephrine. In addition, the current study utilized spontaneous BP fluctuations to assess vascular sympathetic BRS. This technique does not allow for the full baroreflex blood pressure range to be investigated. Despite this, it does allow for BRS analysis around the operating point, and has been found to be well correlated to the modified Oxford technique (Hart et al. 2010). Furthermore, we examined baroreflex function during the Valsalva maneuver. Although there may be limitations with analyzing shorter nerve recording segments (Notay et al. 2016), it is interesting to note that vascular sympathetic baroreflex function was not different between groups both at rest or during the Valsalva, whereas cardiovagal BRS was lower both at rest and during the Valsalva in +FH women. Nevertheless, the results of the current investigation provide valuable new insight into BP control in young +FH women.

In conclusion, young normotensive women with a +FH of hypertension display reduced cardiovagal BRS. However, vascular sympathetic BRS was not different between groups. Given the prognostic value of cardiovagal BRS (Kiviniemi et al. 2014), these data are important in understanding the mechanisms contributing to the greater prevalence of hypertension in those with a familial predisposition.

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AUTHOR CONTRIBUTIONS

ELM, KNS, and MMW performed the experiments; ELM, KNS, and MMW analyzed the data; ELM, KNS, and MMW interpreted the results of the experiments; ELM, KNS, and MMW prepared the figures; KNS and MMW contributed to the conception and design of the research; ELM, KNS, and MMW drafted the manuscript; ELM, KNS, and MMW edited and revised the manuscript; ELM, KNS, and MMW approved the final version of the manuscript.

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DISCLOSURES

None

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FIGURE LEGENDS

Figure 1: Cardiovagal BRS during Phase IV of the Valsalva maneuver in women without (-FH, n=13) and with (+FH, n=12) a family history of hypertension. Group data are shown as mean±SE (top). Individual regression analyses are shown from a representative -FH (middle) and +FH (bottom) woman. *$P < 0.05$

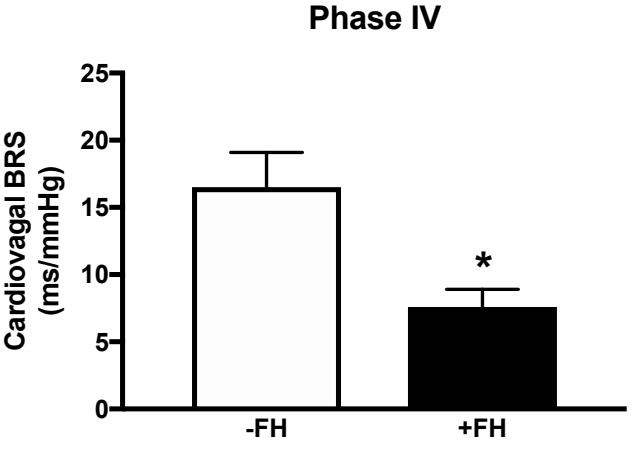
Figure 2: Cardiovagal BRS during Phase II of the Valsalva maneuver in women without (-FH, n=13) and with (+FH, n=12) a family history of hypertension. Group data are shown as mean±SE (top). Individual regression analyses are shown from a representative -FH (middle) and +FH (bottom) woman. *$P < 0.05$

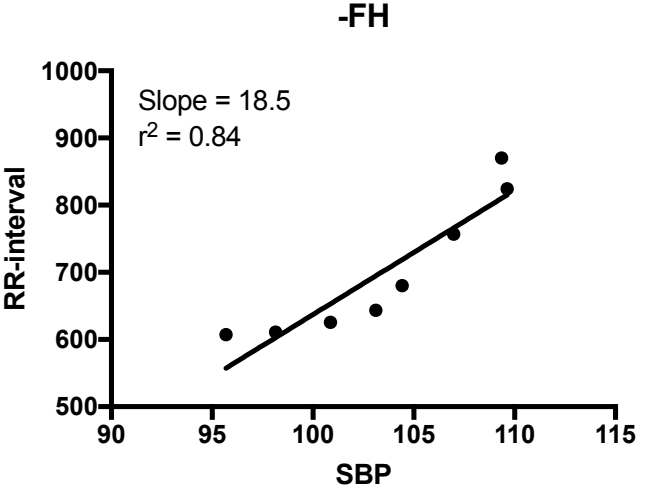
Figure 3: Vascular sympathetic BRS during the Valsalva maneuver in women without (-FH, n=8) and with (+FH, n=8) a family history of hypertension.

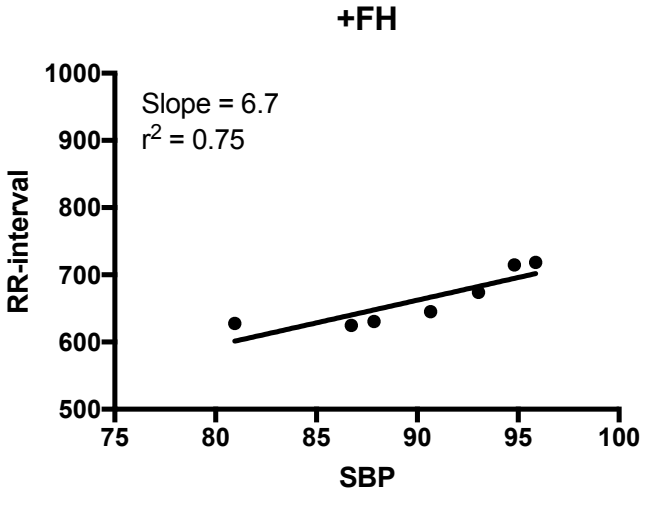
Table 1: Subject Characteristics

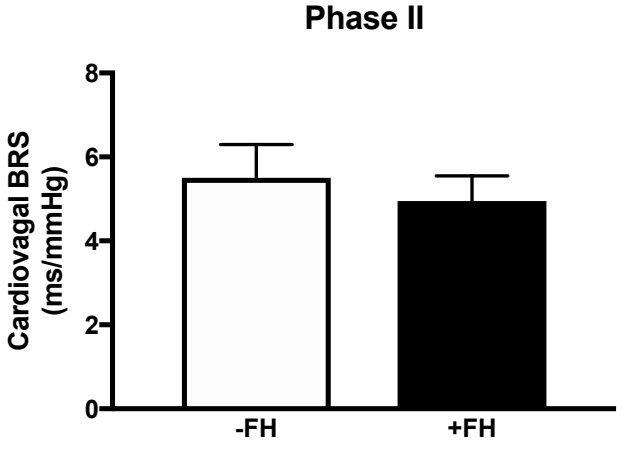
	-FH (n=13)	**+FH (n=12)**
Age (years)	22 ± 1	22 ± 1
Height (cm)	167 ± 2	164 ± 1
Mass (kg)	59 ± 3	58 ± 2
BMI (kg/m^2)	21 ± 1	21 ± 1
SBP (mmHg)	105 ± 2	107 ± 2
DBP (mmHg)	63 ± 2	65 ± 1
MAP (mmHg)	77 ± 2	79 ± 1
HR (bpm)	62 ± 1	69 ± 3

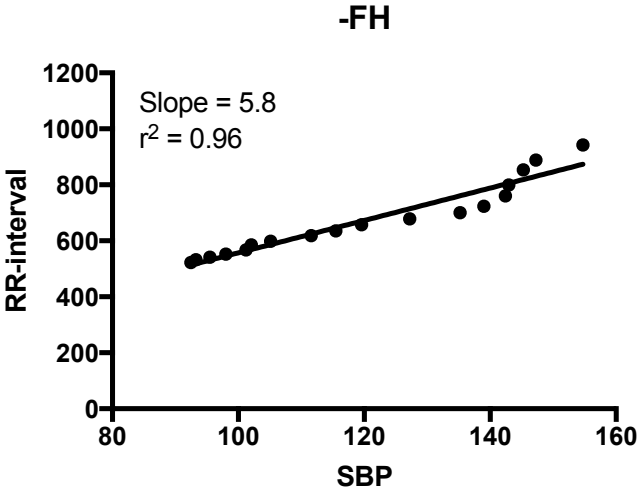
Negative family history of hypertension (-FH), positive family history of hypertension (+FH), body mass index (BMI), diastolic blood pressure (DBP), heart rate (HR), mean arterial pressure (MAP), and systolic blood pressure (SBP). Data are presented as means ± SE.

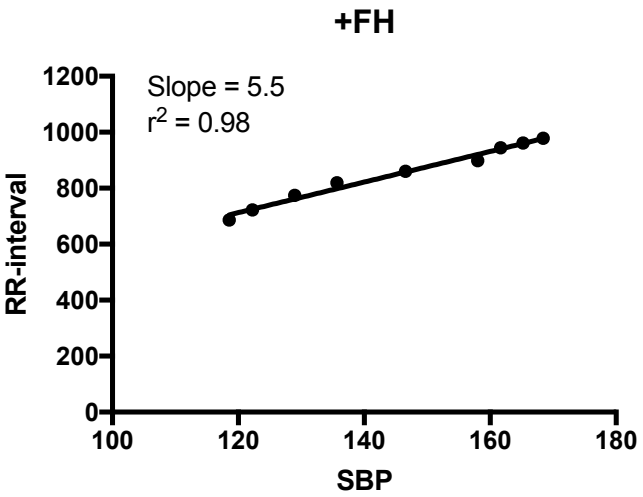

Phase IV
Cardiovagal BRS
(ms/mmHg)
25
20
15
10
5
0
*
-FH
+FH

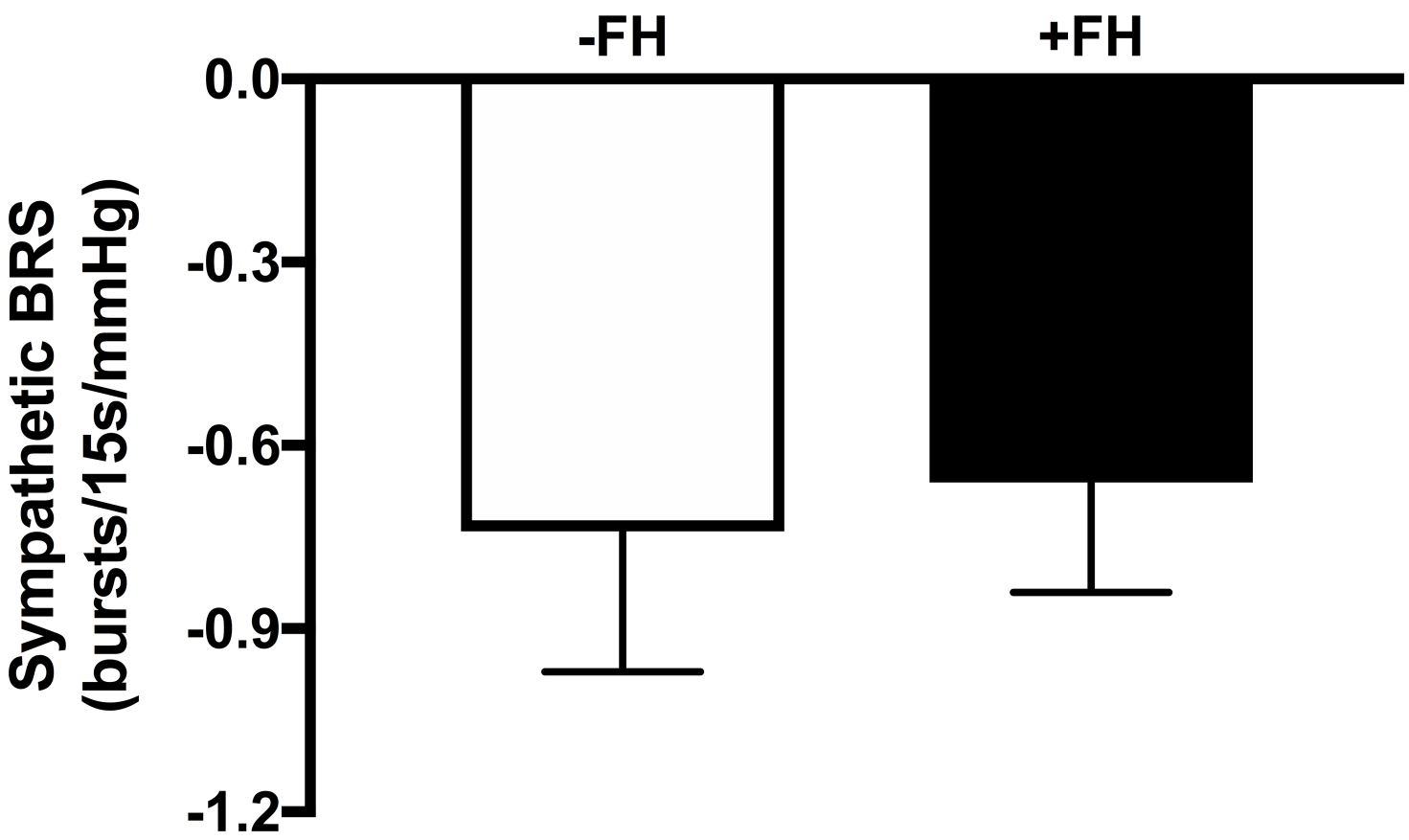

-FH
RR-interval
1000
900
800
700
600
500
Slope = 18.5
r2 = 0.84
90
95
100
105
110
115
SBP


+FH
RR-interval
1000
900
800
700
600
500
Slope = 6.7
r2 = 0.75
75
80
85
90
95
100
SBP


Phase II
Cardiovagal BRS (ms/mmHg)
8
6
4
2
0
-FH
+FH


-FH
RR-interval
Slope = 5.8
r2 = 0.96
1200
1000
800
600
400
200
0
80
100
120
140
160
SBP


+FH
RR-interval
Slope = 5.5
r2 = 0.98
1200
1000
800
600
400
200
0
100
120
140
160
180
SBP


-FH
+FH
0.0
-0.3
-0.6
-0.9
-1.2
Sympathetic BRS
(bursts/15s/mmHg)