CLINICS

CLINICAL SCIENCE

Reproducibility of ambulatory blood pressure changes from the initial values on two different days

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OBJECTIVE: We tested the reproducibility of changes in the ambulatory blood pressure (BP) from the initial values, an indicator of BP reactivity and cardiovascular health outcomes, in young, healthy adults.

METHOD: The subjects wore an ambulatory BP monitor attached by the same investigator at the same time of day until the next morning on two different days (day 1 and day 2) separated by a week. We compared the ambulatory BP change from the initial values at hourly intervals over 24 waking and sleeping hours on days 1 and 2 using linear regression and repeated measures analysis of covariance.

RESULTS: The subjects comprised 88 men and 57 women (mean age $\pm$SE 22.4$\pm$0.3 years) with normal BP (118.3$\pm$0.9/69.7$\pm$0.6 mmHg). For the total sample, the correlation between the ambulatory BP change on day 1 *vs.* day 2 over 24, waking, and sleeping hours ranged from 0.37–0.61; among women, the correlation was 0.38–0.71, and among men, it was 0.24–0.52. Among women, the ambulatory systolic/diastolic BP change was greater by 3.1$\pm$1.0/2.4$\pm$0.8 mmHg over 24 hours and by 3.0$\pm$1.1/2.4$\pm$0.8 mmHg over waking hours on day 1 than on day 2. The diastolic ambulatory BP change during sleeping hours was greater by 2.2$\pm$0.9 mmHg on day 1 than on day 2, but the systolic ambulatory BP change during sleeping hours on days 1 and 2 did not differ. Among men, the ambulatory BP change on days 1 and 2 did not differ.

CONCLUSION: Our primary findings were that the ambulatory BP change from the initial values was moderately reproducible; however, it was more reproducible in men than in women. These results suggest that women, but not men, may experience an alerting reaction to initially wearing the ambulatory BP monitor.

KEYWORDS: Hypertension; Observer Variation; Gender Identity; Clinical Trials as Topic.

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INTRODUCTION

Ambulatory blood pressure (BP) monitoring is the standard clinical method for assessing BP status. Ambulatory BP predicts cardiovascular outcomes and target organ damage, assesses circadian BP patterns, and monitors the response to antihypertensive medication (1,2). However, evidence suggests the prognostic value of ambulatory BP monitoring may be limited to the degree of reproducibility of the BP measurements made on different days (3).

Ambulatory BP reproducibility is defined as the standard deviation of the difference between two BP measurements made on two different days for the same individual. Ambulatory BP reproducibility can also be defined by the coefficient of variation, which is the standard deviation of the difference expressed as a percentage of the mean value of the BP measurements made on two different days. The reported reproducibility between ambulatory BP measurements made on different days differs among studies. For example, the mean standard deviation of the difference in ambulatory BP readings made on two separate days over 24 hours for the same subject has been found to range from 7–13 mmHg for systolic and 3–8 mmHg for diastolic ambulatory BP (4–13). Differences in subject characteristics, such as BP status and age, may explain these apparent inconsistencies and the poor reproducibility of ambulatory BP. Another feature of these studies that could contribute to poor ambulatory BP reproducibility is the long interval of time, typically 3 months or longer, that is often employed between BP measurements (6,8,10,13). In studies that use a long interval between ambulatory BP measurements, reproducibility could be modulated by extraneous factors such as season (14), changes in body weight (1,13), and alterations in adherence to lifestyle behavior patterns and pharmacological therapies used to treat hypertension (1). There is also evidence that the reproducibility of BP

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measurements may be compromised by an alerting reaction to initially wearing the monitor (4,9,11–13,15,16). An alerting reaction is defined as a higher ambulatory BP reading on the first measurement than on the second caused by anxiety and sleep disturbances due to initially wearing the monitor; these disturbances typically diminish upon subsequent ambulatory BP assessments.

We undertook the present study to quantify reproducibility in the change in ambulatory BP from initial values, an indicator of BP reactivity and predictor of cardiovascular health outcomes (17,18), and the average ambulatory BP on 2 separate days 1 week apart in a sample of young, healthy adults with normal BP. We hypothesized that ambulatory BP would be higher on the first day than on the second.

METHODS

Subjects

The participants were recruited from a larger study entitled ''Investigation of whey protein supplementation for physiologic enhancement to resistance training and dietary regimes in young adults'' (REPS) (National Dairy Council 070996). REPS participants were healthy adults 18–35 years of age who had not participated in any resistance training programs during the past year and had resting BP <150/95 mmHg. Prior to participating in REPS, the subjects signed an informed consent form approved by the Institutional Review Board of the University of Connecticut. Upon enrollment, waist circumference was measured at the narrowest part of the torso using a standard flexible tape with a spring-loaded handle (Gulick 4192G, G&S Fibreflex, San Diego, CA). Height was measured with a stadiometer (Seca, Hamburg, Germany), and weight with a calibrated digital scale (OHAUS, Florham Park, NJ). Additionally, the body mass index (BMI) was calculated. Prior to the resistance training and nutrition supplement intervention, the participants were asked to complete two separate ambulatory BP monitoring studies on two different days separated by one week. The ambulatory BP data served as the basis for this sub-study.

Procedures

All ambulatory BP monitoring visits occurred in the morning between 7:00 and 11:00 am (mean ± standard error 9:09 am ± 0:06). The standard procedures used in our previous ambulatory BP studies (2,19–21) were followed and were performed by the same trained investigator at the same time of day for each subject. The subjects were instructed to refrain from formal exercise and caffeine, respectively, 24 hours prior to and the morning of the attachment. Laboratory visits were postponed if the subject was ill, unusually busy or anxious or planned to spend unusual amounts of time in a motorized vehicle the day of the scheduled attachment. Upon entering the laboratory, the subjects were seated for at least 15 minutes. The investigator took a minimum of three BP readings by auscultation in each arm separated by one minute, alternating between the arms, until three auscultatory readings in each arm agreed within 5 mmHg. The investigator then fitted the subject with an appropriately sized BP cuff and attached the Accutracker II automatic non-invasive ambulatory BP monitor (SunTech Medical Instruments Inc., Raleigh, NC). Upon attachment of the monitor, a calibration check was performed using a mercury sphygmomanometer (W.A. Baum Co. Inc., New York, NY) with a t-tubule (2). When three ambulatory BP measurements within 5 mmHg of the auscultatory measurements had been recorded, the ambulatory BP measurements were averaged and reported as the initial BP value for that day.

Upon leaving the laboratory, the subjects were instructed to proceed with normal activities, not to shower or exercise until the next morning, and to keep their arms still and extended when ambulatory BP measurements were being taken. The subjects were asked to carry a standard journal, recording activities performed during each measurement, any unusual physical or emotional events, and sleep and wake times. They were also asked to limit driving while wearing the ambulatory BP monitor; if driving was necessary, they were to rest the cuffed arm against the body at heart level while a reading was being taken.

The ambulatory BP monitor was programmed to record the ambulatory BP every 20 minutes during waking hours and every 30 minutes during sleeping hours to minimize sleep disturbance. The monitor obtained a second reading if there was a difference between consecutive readings of systolic ambulatory BP>50 mmHg, diastolic>40 mmHg, or pulse pressure>50 mmHg. The ambulatory BP recordings were acceptable if the monitor obtained at least 80% of the potential BP readings. Investigators omitted readings if the values met the manufacturer's exclusion criteria of systolic ambulatory BP>220 or <80 mmHg or diastolic>130 or <40 mmHg.

The ambulatory BP readings taken during each hourly interval were averaged to determine the average ambulatory BP for each hour. In the rare instances in which an hourly average interval of ambulatory BP readings was missing, the investigators averaged the BP values from the hours before and after the missed hour to represent the missing data. The initial ambulatory BP was then subtracted from the average ambulatory BP at each hourly time interval to calculate the ambulatory BP change. The 15 hours when the subjects were awake and ambulating represented the waking hours, the 9 hours when the subjects were sleeping represented the sleeping hours, and the 15 waking plus the 9 sleeping hours represented 24 hours. The average and ambulatory BP changes from the initial value were calculated for days 1 and 2 over 24 hours, the waking hours, and the sleeping hours.

Statistical analysis

Descriptive statistics were generated for all dependent and independent variables. Analysis of variance was used to test for differences in the subject descriptive characteristics between the sexes. We used the following statistical methods to assess the reproducibility of the average and ambulatory BP change from the initial value on days 1 *vs.* 2 over 24 hours, the waking hours and the sleeping hours: 1) Pearson correlation coefficients; 2) repeated measures analysis of covariance by sex with BMI and age as covariates; and 3) standard deviation of the difference and coefficient of variation.

Significance was set at $p<0.05$, and all data were reported as the mean ± standard error. All analyses were performed using the Statistical Package for Social Sciences Base 14.0 for Windows (SPSS Inc., Chicago, IL).

Table 1 - Physical characteristics (mean ± standard error) of the study sample by sex.

	Total (n = 145)	Women (n = 57)	Men (n = 88)
Age (yr)	22.4 ± 0.3	22.5 ± 0.5	22.3 ± 0.4
BMI (kg*m^{-2})	25.2 ± 0.4	25.1 ± 0.6	25.2 ± 0.4
Waist Circumference (cm)	78.0 ± 0.9	72.8 ± 1.4	81.4 ± 1.1
Resting Systolic Blood Pressure (mmHg)	118.3 ± 0.9	**112.3 ± 1.3**	**122.3 ± 0.9***
Resting Diastolic Blood Pressure (mmHg)	69.7 ± 0.6	68.9 ± 1.1	70.3 ± 0.7

BMI-body mass index; *$p<0.001$ women *vs.* men. The resting systolic/diastolic blood pressure was calculated as the average of the initial systolic/diastolic blood pressure on days 1 and 2.

RESULTS

Subjects

The characteristics of the participants (57 women, 88 men) are shown in Table 1. Age, BMI, waist circumference, and resting ambulatory diastolic BP were not different between sexes ($p \geq 0.05$). However, the resting ambulatory systolic BP was greater in the men than in the women ($p<0.001$). The two different ambulatory BP measurements were separated by an average of 7.9 ± 0.6 days.

Measures of ambulatory BP reproducibility

Pearson correlation coefficients. Table 2 displays the Pearson correlation coefficients of the ambulatory BP change from the initial value and the average ambulatory BP on day 1 *vs.* day 2 over 24 hours, the waking hours, and the sleeping hours. The correlation between the average ambulatory BP change on day 1 *vs.* day 2 over 24 hours, the waking hours, and the sleeping hours ranged from 0.37–0.61 ($p<0.001$) in the total sample, 0.38–0.71 ($p<0.05$) in women, and 0.24–0.52 ($p<0.01$) in men. The correlation between the average ambulatory BP on days 1 and 2 over 24 hours, the waking hours, and the sleeping hours ranged from 0.62–0.82 ($p<0.001$) in the total sample, 0.74–0.87 ($p<0.001$) in women, and 0.50–0.73 in men ($p<0.001$).

Repeated measures analysis of covariance. Table 3 displays the initial BP, the ambulatory BP change from the initial value, the average ambulatory BP, and the mean differences in these values on day 1 *vs.* day 2 over 24 hours, the waking hours, and the sleeping hours in the total sample and by sex. The initial BP was not different on days 1 and 2 in the total sample or by sex ($p \geq 0.05$).

Among the total sample, the ambulatory BP change from the initial value was greater on day 1 than on 2 over 24 hours for the systolic and diastolic BP ($p = 0.007$ and 0.027, respectively). In addition, the systolic ($p = 0.019$) but not the diastolic ($p \geq 0.05$) ambulatory BP change during the waking hours was greater on day 1 than on day 2. The ambulatory BP change from the initial value over the sleeping hours did not differ on days 1 and 2 ($p \geq 0.05$). The average ambulatory BP over 24 hours was greater on day 1 than on day 2 for both the systolic and diastolic BP ($p = 0.007$ and $p = 0.008$, respectively). In addition, the average systolic ambulatory BP over the waking ($p = 0.014$) and sleeping ($p = 0.047$) hours was greater on day 1 than on day 2, but the average diastolic ambulatory BP over the waking hours did not differ on the 2 days ($p \geq 0.05$).

Among women, the ambulatory BP change for the systolic and diastolic BP was greater on day 1 than on day 2 over 24 hours ($p = 0.004$ and $p = 0.003$, respectively) and over the waking hours ($p = 0.007$ and $p = 0.004$, respectively) (Figure 1). In addition, the women's diastolic ($p = 0.011$) but not systolic ($p \geq 0.05$) ambulatory BP change over the sleeping hours was greater on day 1 than on day 2. Their average ambulatory systolic and diastolic BP was greater on day 1 than on day 2 over 24 hours ($p = 0.005$ and $p = 0.024$, respectively) and during the waking hours ($p = 0.014$ and $p = 0.039$, respectively), and their average systolic ($p = 0.014$) but not diastolic ($p \geq 0.05$) ambulatory BP was greater on day 1 than on 2 during the sleeping hours. In contrast, among

Table 2 - Pearson correlation coefficients between the initial blood pressure, ambulatory blood pressure change from the initial value, and average ambulatory blood pressure on day 1 *vs.* day 2 over 24 hours, the waking hours, and the sleeping hours.

	Total (n = 145)	Women (n = 57)	Men (n = 88)
Initial			
SBP	0.80	0.78	0.73
DBP	0.70	0.82	0.61
Ambulatory BP Change from Initial Values			
24 hour SBP	0.40	0.41*	0.40
24 hour DBP	0.42	0.52	0.38
Awake SBP	0.37	0.38†	0.38
Awake DBP	0.39	0.47	0.36
Sleep SBP	0.61	0.71	0.52
Sleep DBP	0.39	0.63	0.24‡
Average Ambulatory BP			
24 hour SBP	0.82	0.85	0.72
24 hour DBP	0.79	0.87	0.73
Awake SBP	0.81	0.84	0.70
Awake DBP	0.76	0.85	0.68
Sleep SBP	0.71	0.74	0.60
Sleep DBP	0.62	0.78	0.50

All correlations $p<0.001$ unless indicated: *$p = 0.001$, †$p = 0.003$, ‡$p = 0.024$. SBP-systolic blood pressure; DBP-diastolic blood pressure.

Table 3 - Comparison of ambulatory blood pressure changes from the initial values and average ambulatory blood pressure (mmHg) on day 1 *vs.* day 2 over 24 hours, the waking hours, and the sleeping hours (mean±standard error).

	Total (n = 145)					Women (n = 57)					Men (n = 88)				
	Day 1	Day 2	Difference*	Standard Deviation of the Difference	Coefficient of Variation	Day 1	Day 2	Difference*	Standard Deviation of the Difference	Coefficient of Variation	Day 1	Day 2	Difference*	Standard Deviation of the Difference	Coefficient of Variation
Initial															
SBP	117.2±0.8	117.5±0.8	0.3±0.6	3.8±0.3	3.2±0.2	111.7±1.3	112.9±1.3	1.2±0.9	3.7±0.4	3.3±0.3	122.7±0.9	122.1±0.9	−0.6±0.8	3.9±0.3	3.2±0.3
DBP	69.7±0.7	69.9±0.6	0.2±0.5	3.4±0.2	4.8±0.3	68.2±1.1	69.5±1.1	1.3±0.7	2.9±0.4	4.2±0.5	70.7±0.8	70.1±0.7	−0.6±0.7	3.7±0.3	5.4±0.4
Ambulatory BP Change From Initial Values															
24 hour SBP	**6.3±0.6**	**4.5±0.6**	**−1.9±0.7‡**	4.5±0.3		**7.0±1.0**	**3.9±1.0**	**−3.1±1.0‡**	4.3±0.5		5.6±0.8	5.0±0.8	−0.6±0.9	4.5±0.4	
24 hour DBP	**0.5±0.5**	**−0.7±0.5**	**−1.2±0.6†**	3.6±0.3		**1.4±0.7**	**−1.0±0.8**	**−2.4±0.8‡**	3.4±0.4		−0.3±0.7	−0.4±0.6	−0.1±0.8	3.8±0.3	
Awake SBP	**12.0±0.7**	**10.3±0.7**	**−1.7±0.7†**	4.9±0.3		**12.5±0.9**	**9.5±1.0**	**−3.0±1.1‡**	4.6±0.5		11.5±0.9	11.1±0.8	−0.5±1.0	5.1±0.4	
Awake DBP	5.7±0.6	4.5±0.5	−1.2±0.6	3.8±0.3		**6.7±0.8**	**4.2±0.8**	**−2.5±0.8‡**	3.7±0.5		5.1±0.8	4.8±0.6	−0.4±0.8	3.9±0.4	
Sleep SBP	−4.2±0.8	−5.3±0.9	−1.1±0.8	4.5±0.4		−3.2±1.3	−4.7±1.4	−1.5±1.1	3.9±0.6		−5.2±1.0	−5.9±1.1	−0.7±1.0	5.0±0.5	
Sleep DBP	−9.5±0.6	−10.2±0.6	−0.7±0.7	4.6±0.3		**−8.6±1.0**	**−10.8±1.0**	**−2.2±0.9†**	3.7±0.5		−10.1±0.9	−9.7±0.8	0.4±1.0	5.3±0.4	
Average Ambulatory BP															
24 hour SBP	**123.5±0.8**	**122.0±0.7**	**−1.5±0.5‡**	3.3±0.3	2.6±0.2	**118.7±1.2**	**116.8±1.1**	**−1.9±0.7‡**	3.0±0.4	2.5±0.3	128.2±1.0	127.2±0.8	−1.0±0.8	3.5±0.3	2.7±0.2
24 hour DBP	**70.0±0.5**	**69.1±0.5**	**−0.9±0.3‡**	2.2±0.2	3.2±0.2	**69.6±0.8**	**68.5±0.9**	**−1.0±0.5†**	2.1±0.2	3.1±0.3	70.4±0.7	69.6±0.6	−0.8±0.5	2.3±0.2	3.2±0.3
Awake SBP	**129.2±0.8**	**127.8±0.7**	**−1.4±0.6†**	3.6±0.3	2.8±0.2	**124.2±1.3**	**122.3±1.2**	**−1.8±0.7†**	3.3±0.4	2.7±0.3	134.2±1.0	133.2±0.9	−1.0±0.8	3.9±0.3	2.8±0.3
Awake DBP	75.5±0.6	74.4±0.6	−1.1±0.4	2.7±0.2	3.6±0.3	**74.9±1.0**	**73.7±1.0**	**−1.1±0.5†**	2.5±0.3	3.4±0.4	75.9±0.8	74.9±0.7	−1.0±0.6	2.9±0.2	3.7±0.3
Sleep SBP	**112.9±0.9**	**111.5±0.8**	**−1.5±0.7†**	4.5±0.3	3.8±0.3	**108.5±1.3**	**106.1±1.2**	**−2.4±0.9†**	3.8±0.5	3.5±0.4	117.4±1.2	116.8±1.0	−0.6±1.0	4.9±0.4	4.1±0.4
Sleep DBP	60.1±0.5	59.6±0.5	−0.5±0.5	3.2±0.2	5.1±0.3	59.6±0.8	58.6±0.9	−1.0±0.6	2.6±0.3	4.5±0.5	60.4±0.7	60.3±0.7	−0.1±0.7	3.5±0.3	5.8±0.4

SBP-systolic blood pressure; DBP-diastolic blood pressure. *Difference indicates significance for day 1 *vs.* day 2 based on the repeated measures analysis of covariance. †$p<0.05$, ‡$p<0.01$.
We do not report the coefficient of variation for the ambulatory BP change because the ambulatory BP change adjusts for the initial BP value, as does the coefficient of variation.

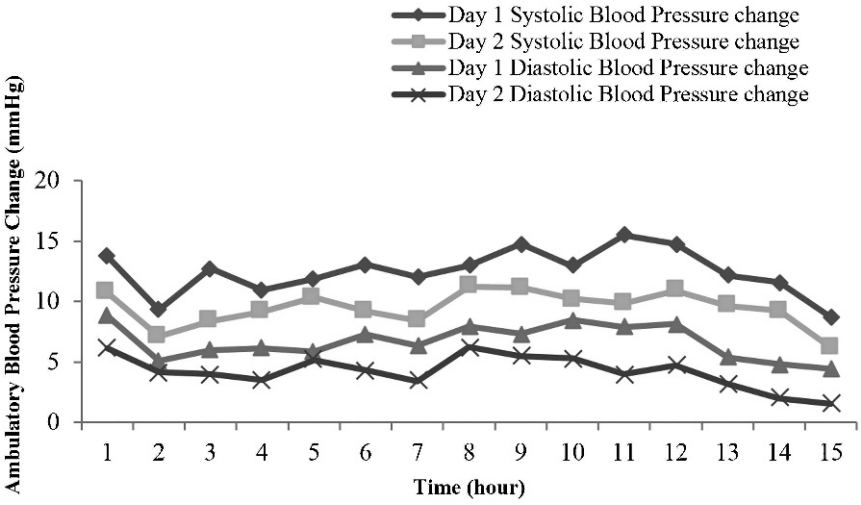

Figure 1 - Average waking ambulatory blood pressure change from the initial value at hourly intervals over 15 hours on 2 different days separated by 1 week among women.

men, the ambulatory BP change from the initial value and the average ambulatory BP did not differ on days 1 and 2 over 24 hours, the waking hours, and the sleeping hours ($p \geq 0.05$).

Standard deviation of the difference and coefficient of variation. Table 3 also reports the standard deviation of the difference and the coefficient of variation for the initial BP, the ambulatory BP change from the initial value, and the average ambulatory BP on days 1 *vs.* 2 over 24 hours, the waking hours and the sleeping hours in the total sample and by sex. The standard deviation of the difference in the ambulatory BP change from the initial value on day 1 *vs.* day 2 over 24 hours, the waking hours, and the sleeping hours ranged from 3.6–4.9 mmHg in the total sample, 3.4–4.6 mmHg in women, and 3.8–5.3 mmHg in men. The standard deviation of the difference in the average ambulatory BP on day 1 *vs.* day 2 over 24 hours, the waking hours, and the sleeping hours ranged from 2.2–4.5 mmHg in the total sample, 2.1–3.8 mmHg in women, and 2.3–4.9 mmHg in men.

The coefficient of variation between the average ambulatory BP on day 1 *vs.* day 2 over 24 hours, the waking hours, and the sleeping hours ranged from 2.6–4.5% in the total sample, 2.5–4.5% in women, and 2.7–5.8% in men. We do not report the coefficient of variation for the ambulatory BP change because the ambulatory BP change adjusts for the initial BP values, as does the coefficient of variation.

DISCUSSION

Our primary findings were that the average ambulatory BP was strongly reproducible and that the ambulatory BP change from the initial value was moderately reproducible when measured in young, healthy subjects with normal BP on 2 different days separated by 1 week. An unexpected finding was that the average ambulatory BP was 1–2 mmHg higher and the ambulatory BP change from the initial value was 2–3 mmHg higher on day 1 *vs.* day 2 among the women but not among the men. This finding suggests that women, but not men, may have experienced an alerting reaction to initially wearing the ambulatory BP monitor (15,16).

Our study is unique because we assessed not only the reproducibility of average ambulatory BP but also ambulatory BP change from initial value as indicators of reproducibility. Based upon strength of the correlations reported in Table 2 and the smaller standard deviation of the difference reported in Table 3, average ambulatory BP appears to be more reproducible than ambulatory BP change. Stergiou and Parati (18) recently stated that the ambulatory BP change from the initial value, which they termed 'BP reactivity', was a better indicator of the physiologic response to wearing an ambulatory BP monitor under conditions of daily living than average ambulatory BP. Furthermore, evidence suggests that BP reactivity predicts cardiovascular health outcomes independent of initial BP value (17). For example, the Coronary Artery Risk Development in Young Adults (CARDIA) study measured the BP change from the initial value among young adult women and men in response to playing a video game (22). The CARDIA investigators found that for each 10 mmHg systolic BP increase from the initial value, there was a 24% increased likelihood of developing subsequent coronary artery calcification within 13 years. Thus, determining the reproducibility of not only the measurement of average ambulatory BP but also the ambulatory BP change from the initial value appears to be important.

Our study confirms the findings reported in the existing literature that the average ambulatory BP is strongly reproducible among study populations with normal BP regardless of whether the ambulatory BP measurements are separated by several weeks (11) or months (8). We found that the standard deviation of the difference in the average ambulatory BP ranged from 2–4 mmHg and that its coefficient of variation ranged from 3–5% among the subjects in our study who had normal BP (Table 3). In contrast, studies that included subjects with hypertension found higher standard deviation of the difference values ranging from 4–13 mmHg, independent of whether ambulatory BP measurements were separated by several weeks (4,5,7,9,12) or by several months (6,10,13). The greater BP variability among individuals with a higher BP is consistent with recent findings that visit-to-visit (23,24) and

within-visit (25) BP variability for resting BP correlates positively with BP status.

The higher ambulatory BP readings observed on day 1 *vs.* day 2 among women but not among men suggest that the women, but not the men, experienced an alerting reaction to initially wearing the monitor (15,16). Shin et al. (25) found that women exhibited greater within-visit auscultatory BP variability than men, including greater differences between the initial and subsequent BP measurements; this effect was considered to result from an alerting reaction to the initial auscultatory BP measurement. Calvo et al. (15) found that when women and men with hypertension wore an ambulatory BP monitor continuously for 48 hours, the average ambulatory BP over 24 hours and the waking hours was lower on the second day than on the first day. Consistent with these findings, Palatini et al. (13) reported that when women and men with hypertension completed two ambulatory BP monitoring studies separated by three months, the average ambulatory BP declined by 1 mmHg. Similarly, Musso et al. (16) found that when women and men with a normal BP completed four ambulatory BP monitoring studies, each separated by one week, the average ambulatory BP declined approximately 1 mmHg with each successive weekly measurement, reaching statistical significance by the fourth week. Trazzi et al. (4) and Coats et al. (12) also documented trends in ambulatory BP reductions between successive readings, although the reductions did not reach statistical significance.

Our study is the first to show that an alerting reaction appears to be gender-dependent and that such a reaction can significantly affect the reproducibility of ambulatory BP. These findings are relevant to both clinical practice and research. For our results indicate that a familiarization ambulatory BP session should occur prior to any clinical decision making regarding the interpretation of the BP response to an experimental perturbation, and perhaps the effectiveness of antihypertensive therapy. A difference in the BP response of 2–3 mmHg, such as we found between the first and second ambulatory BP monitoring studies, could be mistakenly attributed to experimental intervention or antihypertensive treatment when, in fact, it might be due to an alerting reaction to wearing the ambulatory BP monitor for the first time (26).

A question raised by our findings of a sex-dependent response is why an alerting reaction was experienced by the women but not by the men. Steptoe et al. (27) found that men exhibited a greater BP response to mental stress interventions administered in the laboratory than did women. Furthermore, laboratory experiments indicate that sympathetic nerve activity is positively associated with BP in men; however, if an association is found among women, it is in the opposite direction to that of men (28,29). In addition, it would seem the men in our study would be more susceptible to experiencing greater BP variability between ambulatory BP measurements made on different days due to having higher resting BP than the women (23–25). Collectively, these data suggest that the men in our study would have been more likely to experience an alerting reaction to initially wearing the ambulatory BP monitor, whereas we observed the opposite.

Previous studies addressing ambulatory BP reproducibility on 2 different days have not found sex differences, possibly due to the use of small sample sizes (4,6–12) and/or the use of intervals of 3 months or longer between the BP measurements (6,8,10,13). However, Muntner et al. (23) found that women exhibited higher day-to-day variability in auscultatory systolic BP than men, findings that are consistent with ours. Similarly, Shin et al. (25) found that women exhibited a higher within-visit variability in auscultatory systolic and diastolic BP measurements than men. State anxiety (30), psychological distress (31), and social alienation (31) influence BP more strongly in women than in men and may drive the sex differences in BP variability. Sex differences in state anxiety also partially explain the higher 'white-coat hypertension' among women than men (30,32,33). Although we did not measure sympathetic nerve activity, the differences we observed in ambulatory BP on day 1 *vs.* day 2 were not accompanied by significant differences in the heart rate ($p \geq 0.05$, data not shown), suggesting that sex-dependent differences in sympathetic nerve activity do not account for our findings. Hypothalamic-pituitary-adrenal cortical stress reactivity directly correlates with BP stress reactivity (34) and is higher among women than men (35). Therefore, sex differences in cortical system stress reactivity are a plausible physiological mechanism that may underlie the sex differences in the day-to-day BP variability that we and others have observed (23,25,30,32,33). Future mechanistic studies are required to evaluate this possibility and to evaluate other possible mechanisms.

A major limitation of our study is that, on average, our subjects had normal BP. We do not know whether our findings regarding the lower reproducibility of ambulatory BP in women than in men are generalizable to individuals with hypertension. Several investigators found a higher ambulatory BP on day 1 *vs.* day 2 among subjects with hypertension but no sex differences in the reproducibility, possibly due to the use of small sample sizes (4,9,12) and/or long (3-month) intervals between BP measurements (13). Based on previous reports that ambulatory BP reproducibility is lower (4–7,9,10,12,13) and overall BP variability is higher (23–25) in subjects with hypertension than in subjects with normal BP (8,11), we would expect the ambulatory BP to be even less reproducible among women with hypertension than we found to be the case for young women with normal BP. However, further work is needed to determine whether this supposition is correct.

In summary, the average ambulatory BP was strongly reproducible, and the ambulatory BP change from the initial value was moderately reproducible in a large sample of young adults with normal BP. A new and unexpected finding was that women, but not men, experienced an alerting reaction of 1–3 mmHg during the initial period of wearing the ambulatory BP monitor. Our observations support the contention that visit-to-visit variability in BP is affected more in women than in men by integrated, complex physiological responses to psychosocial factors (18). The effect we observed could be mitigated by the inclusion of a familiarization ambulatory BP measurement performed prior to the measurements aimed at evaluating the effects of experimental interventions or treatments.

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AUTHOR CONTRIBUTIONS

Gomez AL, Kraemer WJ, Volek JS, and Pescatello LS participated in the study design. Ash GI, Walker TJ, Olson KM, Gomez AL, Kraemer WJ, Volek JS, and Pescatello LS conducted the study. Ash GI, Stratton JH, and Pescatello LS performed the statistical analysis. Ash GI, Walker TJ, Olson KM, and Pescatello LS drafted and reviewed the manuscript. All authors reviewed and approved the manuscript.

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