HHS Public Access

Author manuscript

*J Hum Hypertens*. Author manuscript; available in PMC 2024 August 01.

Published in final edited form as:

*J Hum Hypertens*. 2023 August ; 37(8): 742–745. doi:10.1038/s41371-023-00824-y.

# Association of Blood Pressure Variability with Endothelin-1 by Menopause Status among Black Women: Findings from the Jackson Heart Study

**Leah Rethy, MD**[1], **Vincenzo B. Polsinelli, MD**[2], **Paul Muntner, PhD**[3], **Natalie A. Bello, MD, MPH**[4], **Jordana B. Cohen, MD, MSCE**[5]

[1]Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA.

[2]Division of Cardiology, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO.

[3]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL.

[4]Department of Cardiology, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA.

[5]Renal-Electrolyte and Hypertension Division, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA.

## Abstract

Postmenopausal women have a higher risk of hypertension compared with premenopausal women possibly related to increased endothelial dysfunction in the setting of lower levels of circulating estrogen. Using data from 660 women in the Jackson Heart Study (JHS), postmenopausal women had higher daytime, nighttime and 24-hour systolic blood pressure variability (BPV) compared with premenopausal women, and higher nighttime systolic BPV was associated with higher endothlin-1 (a marker of endothelial dysfunction) in postmenopausal women (ß =0.27 [0.05, 0.50], p=0.019), even after adjustment for possible confounders including age. These findings highlight the relevance of menopause status to blood pressure variability and the potential role of blood pressure variability in the development of high endothelin-1 in postmenopausal women.

Postmenopausal women have a higher risk of hypertension and hypertension-related cardiovascular disease (CVD) than premenopausal women and this risk is especially high among Black women [1]. Blood pressure (BP) variability (BPV) is associated with oxidative stress and endothelial dysfunction and there is evidence that postmenopausal women have increased BPV as well as increased markers of endothelial dysfunction [2,3]. The association between BPV and endothelial dysfunction in postmenopausal women has

**Address for correspondence:** Jordana Cohen, MD, MSCE, 423 Guardian Drive, Blockley Hall 831, Philadelphia, PA 19104, jco@pennmedicine.upenn.edu.

**Author Contributions:** LR and JC were responsible for all aspects for the study including study concept, study design, data acquisition, data analysis and manuscript drafting. PM and NB were involved in the study design, data interpretation as well as critical revision of the paper. VP provided critical revision. All authors provided final approval.

**Ethical Approval:** All participants in the Jackson Heart Study provided informed consent and the University of Mississippi Medical Center, Jackson State University, and Tougaloo College institutional review boards approved the study.

been underexplored [4,5]. We examined the association between BPV and endothelin-1, a vasoconstrictor implicated in endothelial dysfunction and hypertension, among pre- and postmenopausal women in the Jackson Heart Study (JHS) [6].

Design, methods, and baseline characteristics of the JHS have been previously detailed [7]. Briefly, JHS is a longitudinal, population-based cohort study of CVD among Black adults aged 21-95 years at baseline in the Jackson, Mississippi metropolitan area [7]. All participants provided informed consent and the University of Mississippi Medical Center, Jackson State University, and Tougaloo College institutional review boards approved the study. The study population for this cross-sectional analysis included 660 women who had 1) complete ambulatory BP monitoring (ABPM) recordings defined by ≥70% valid readings, 2) endothelin-1 values and 3) responded to the question "Have you had any menstrual periods or bleeding during the past 2 years." A "no" response to this question defined postmenopausal status [8,9]. Participants who underwent ABPM had a portable oscillometric device (Spacelabs 90207, Spacelabs) attached to their nondominant arm. The device was calibrated by trained technicians after placement and BP readings were programmed to be taken every 20 minutes for 24 hours. Endothlin-1 levels were measured in participants after an overnight fast and were quantified using ELISA (enzyme-linked immunosorbent assay) in picograms per milliliter (QuantiGlo Human ET-1 Immunoassay [R&D Systems Inc]). Covariates were chosen *a priori* and classification of BP readings as daytime or nighttime was based on International Database of ABP in relation to Cardiovascular Outcome (IDACO) criteria (nighttime: 00:00-06:00, daytime: 10:00-20:00) [10].

We defined BPV using average real variability (ARV), the sum of absolute differences between successive BP readings divided by the total number of readings minus one, for 24-hour, daytime and nighttime systolic BP (SBP) and diastolic BP (DBP), separately [5,11]. Descriptive statistics were calculated by menopause status and compared using $\chi^2$ tests, two-sample t-tests or Wilcoxon rank-sum tests, as appropriate. In linear regression models stratified by menopause status, we assessed the association of endothelin-1 with BPV. Given a non-normal distribution, endothelin-1 levels were log-transformed and then standardized. Model 1 adjusted for mean BP (SBP and DBP—daytime, nighttime, 24-hour for each respective BPV metric [e.g. daytime SBP BPV adjusted for mean daytime SBP]), antihypertensive medication use, prevalent CVD (stroke or coronary heart disease), total cholesterol, smoking status, and diabetes. Model 2 additionally adjusted for estimated glomerular filtration rate (eGFR) calculated using the non-race CKD-EPI Creatinine Formula [2021] and model 3 additionally adjusted for age. In supplemental analyses restricted to postmenopausal women, we adjusted model 3 further for (1) hormone replacement therapy (HRT) and (2) premature menopause (<40 years). Multiple imputation by chained equations (10 iterations) was used for missing data and statistical significance was defined by a 2-sided p-value <0.05. Given the exploratory nature of the analyses, p-values were not corrected for multiple comparisons.

Of the 660 women included in this analysis, 531 (80.5%) were postmenopausal. Postmenopausal women were older (62 ± SD: 9 years vs. 47 ±10 years), more likely to be taking antihypertensive medication (66% vs. 38%), have a history of diabetes (29% vs. 15%), have a lower median eGFR (82 [$25^{th}$-$75^{th}$ percentiles: 71, 94] ml/min/1.73$m^2$ vs. 96

[80, 108] ml/min/1.73m$^2$) and have higher median endothelin-1 levels (25$^{th}$-75$^{th}$ percentiles: 1.2 [0.9, 1.6] pg/mL vs. 1.1 [0.8, 1.3] pg/mL) than premenopausal women (each p<0.05, FIGURE). Also, 10% and 6% of postmenopausal and premenopausal women, respectively, had a history of CVD (p=0.15). Median (25$^{th}$-75$^{th}$ percentile) daytime and nighttime SBP were higher in postmenopausal vs. premenopausal women but median DBP did not differ between groups (FIGURE). Daytime SBP ARV, nighttime SBP ARV and 24-hour SBP ARV were each higher in postmenopausal vs. premenopausal women (median [25$^{th}$ – 75$^{th}$ percentile] SBP ARV: daytime: 9.9 [8.0, 11.7] vs. 8.6 [7.1, 10.2], p<0.001; nighttime: 8.0 [6.4, 9.7] vs. 7.3 [6.0, 8.6], p<0.001; 24-hour: 9.0 [7.8, 10.4] vs. 8.1 [7.0, 9.2], p=0.001). In unadjusted models, for every SD higher log endothelin-1 level there was a 0.32 [95% CI: 0.09, 0.55] times higher SBP ARV (p=0.007, FIGURE); this association was present in the fully adjusted model (ß =0.27 [95% CI 0.05, 0.50], p=0.019). Endothelin-1 was not associated with any measure of DBP ARV or 24-hour or daytime SBP ARV. Associations between BPV and endothelin-1 were similar after adjusting for HRT use and premature menopause among postmenopausal women; nighttime SBP ARV and endothlin-1 remained associated after these additional adjustments (ß =0.26 [0.01 , 0.51], p=0.04). There was no evidence of an association between endothelin-1 and SBP or DBP ARV in premenopausal women.

In the current study, higher endothelin-1 levels were associated with higher nighttime SBP ARV in postmenopausal Black women after adjustment for potential confounders including age. This study builds on prior studies by linking endothelin-1 levels and higher nighttime SBP BPV in postmenopausal women. This is notable given that nighttime SBP BPV has been previously shown to have a stronger association with adverse cardiovascular outcomes compared with daytime and 24-hour BPV [12]. The stronger association of nighttime BPV with adverse cardiovascular outcomes is likely due the more prominent role of adverse endogenous factors (e.g. vascular dysfunction, elevated endothelin-1 levels) in determining BPV while individuals are asleep or resting [12]. This study was limited by the small number of premenopausal women and by the multiple comparisons made. In addition, the cross-sectional nature of the analysis limits the ability to assess causality or the directionality of the relationship between endothelin-1 and SBP ARV in postmenopausal women. In conclusion, these findings demonstrate the value of assessing nighttime BPV in postmenopausal women and underscore the possible role of endothelin-1 in the development of abnormal BP patterns. Future studies could consider interventions to lower endothelin-1in post-menopausal women.

## Funding:

The Jackson Heart Study (JHS) is supported and conducted in collaboration with Jackson State University (HHSN268201800013I), Tougaloo College (HHSN268201800014I), the Mississippi State Department of Health (HHSN268201800015I) and the University of Mississippi Medical Center (HHSN268201800010I, HHSN268201800011I and HHSN268201800012I) contracts from the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute on Minority Health and Health Disparities (NIMHD).

**Competing Interests:**

There are no competing interests for any of the authors. JC is supported by the National Institutes of Health K23-HL133843, R01-HL153646, R01-HL157108, R01-HL155599, R01-HL157264, U01-HL160277, U24-DK060990, and R01-AG074989, and an American Heart Association Bugher Award. The views expressed in this manuscript

are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services.

## REFERENCES:

1. Wenger NK, Arnold A, Bairey Merz CN, Cooper-DeHoff RM, Ferdinand KC, Fleg JL et al. Hypertension Across a Woman's Life Cycle. J Am Coll Cardiol 71, 1797–1813 (2018). 10.1016/j.jacc.2018.02.033 [PubMed: 29673470]
2. Migneco A, Ojetti V, Covino M, Mettimano M, Montebelli MR, Leone A et al. Increased blood pressure variability in menopause. Eur Rev Med Pharmacol Sci 12, 89–95 (2008). [PubMed: 18575158]
3. Shimbo D, Wang L, Lamonte MJ, Allison M, Wellenius GA, Bavry AA et al. The effect of hormone therapy on mean blood pressure and visit-to-visit blood pressure variability in postmenopausal women: results from the Women's Health Initiative randomized controlled trials. J Hypertens 32, 2071–2081; discussion 2081 (2014). 10.1097/hjh.0000000000000287 [PubMed: 24991872]
4. Coylewright M, Reckelhoff JF & Ouyang P Menopause and hypertension: an age-old debate. Hypertension 51, 952–959 (2008). 10.1161/hypertensionaha.107.105742 [PubMed: 18259027]
5. Mena LJ, Felix VG, Melgarejo JD & Maestre GE 24-Hour Blood Pressure Variability Assessed by Average Real Variability: A Systematic Review and Meta-Analysis. J Am Heart Assoc 6 (2017). 10.1161/jaha.117.006895
6. Reckelhoff JF & Fortepiani LA Novel mechanisms responsible for postmenopausal hypertension. Hypertension 43, 918–923 (2004). 10.1161/01.Hyp.0000124670.03674.15 [PubMed: 15023933]
7. Fuqua SR, Wyatt SB, Andrew ME, Sarpong DF, Henderson FR, Cunningham MF et al. Recruiting African-American research participation in the Jackson Heart Study: methods, response rates, and sample description. Ethnicity & disease 15, S6-18–29 (2005).
8. O'Brien E, Parati G, Stergiou G, Asmar R, Beilin L, Bilo G et al. European Society of Hypertension position paper on ambulatory blood pressure monitoring. J Hypertens 31, 1731–1768 (2013). 10.1097/HJH.0b013e328363e964 [PubMed: 24029863]
9. Campbell Jenkins BW, Addison C, Wilson G, Liu J, Fortune M, Robinson K et al. Association of the joint effect of menopause and hormone replacement therapy and cancer in African American women: the Jackson Heart Study. International journal of environmental research and public health 8, 2491–2504 (2011). 10.3390/ijerph8062491 [PubMed: 21776241]
10. Thijs L, Hansen TW, Kikuya M, Björklund-Bodegård K, Li Y, Dolan E et al. The International Database of Ambulatory Blood Pressure in relation to Cardiovascular Outcome (IDACO): protocol and research perspectives. Blood Press Monit 12, 255–262 (2007). 10.1097/mbp.0b013e3280f813bc [PubMed: 17760218]
11. Mena L, Pintos S, Queipo NV, Aizpurua JA, Maestre G & Sulbaran T A reliable index for the prognostic significance of blood pressure variability. J Hypertens 23, 505–511 (2005). [PubMed: 15716690]
12. Palatini P, Reboldi G, Beilin LJ, Casiglia E, Eguchi K, Imai Y et al. Added predictive value of night-time blood pressure variability for cardiovascular events and mortality: the Ambulatory Blood Pressure-International Study. Hypertension 64, 487–493 (2014). 10.1161/HYPERTENSIONAHA.114.03694 [PubMed: 24935939]

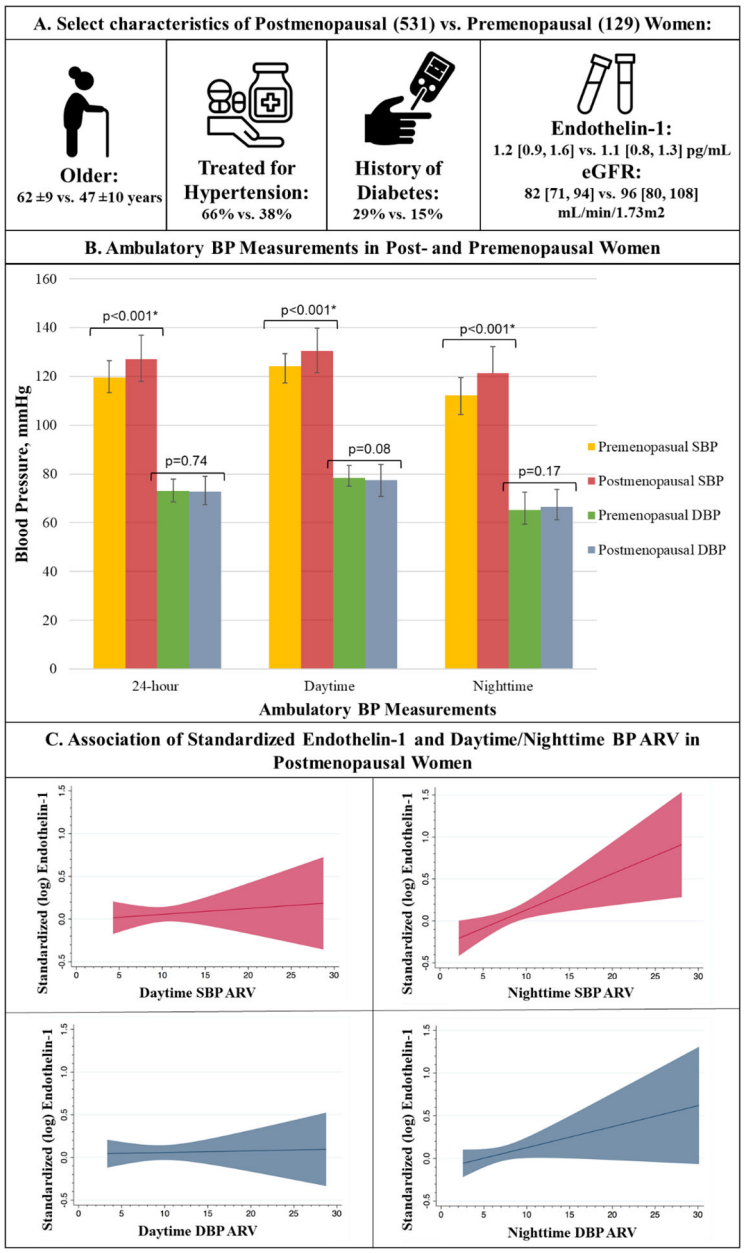


**FIGURE. Ambulatory Blood Pressure Monitoring, Endothelin-1 and Menopause Status in the Jackson Heart Study.**

Panel A presents select characteristics in postmenopausal vs. premenopausal women as mean ±standard deviation, %, or median [25$^{th}$-75$^{th}$ percentile]. Panel B presents the median [25$^{th}$-75$^{th}$ percentile] for 24-hour, daytime and nighttime systolic and diastolic blood pressure by menopause status, p-values presented for each comparison using Wilcoxon rank sum tests. * indicates a significant difference ($p<0.05$) in average real variability (ARV) for each ambulatory blood pressure metric (e.g. 24-hour SBP ARV is significantly different in postmenopausal compared with premenopausal women). Panel C presents the association between daytime and nighttime SBP and DBP ARV with standardized endothelin-1 for postmenopausal women, the solid line represents the estimate and the shaded area presents

the 95% confidence interval. Endothlin-1 is log transformed given a non-normal distribution. ARV: average real variability; BP: blood pressure; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate, calculated using the 2021 CKD-EPI creatinine equation; SBP: systolic blood pressure.