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Published in:
Journal of Hypertension

DOI:
10.1097/HJH.0000000000002988

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Xu, Y., Su, S., Brown, M., Snieder, H., Harshfield, G., & Wang, X. (2022). Ethnic differences and heritability of blood pressure circadian rhythm in African and European American youth and young adults. *Journal of Hypertension*, *40*(1), 163-170. https://doi.org/10.1097/HJH.0000000000002988

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Original Article

Ethnic differences and heritability of blood pressure circadian rhythm in African and European American youth and young adults

Yanyan Xu[a,b], Shaoyong Su[a], Michelle Brown[a], Harold Snieder[a,c], Gregory Harshfield[a], and Xiaoling Wang[a,b]

Background: The aim of this study was to investigate whether blood pressure (BP) circadian rhythm in African Americans differed from that in European Americans. We further examined the genetic and/or environmental sources of variances of the BP circadian rhythm parameters and the extent to which they depend on ethnicity or sex.
Method: Quantification of BP circadian rhythm was obtained using Fourier transformation from the ambulatory BP monitoring data of 760 individuals (mean age, 17.2 ± 3.3; 322 twin pairs and 116 singletons; 351 African Americans).
Results: BP circadian rhythm showed a clear difference by ethnic group with African Americans having a lower amplitude ($P = 1.5e{-}08$), a lower percentage rhythm ($P = 2.8e{-}11$), a higher MESOR ($P = 2.5e{-}05$) and being more likely not to display circadian rhythm ($P = 0.002$) or not in phase ($P = 0.003$). Familial aggregation was identified for amplitude, percentage rhythm and acrophase with genetic factors and common environmental factors together accounting for 23 to 33% of the total variance of these BP circadian rhythm parameters. Unique environmental factors were the largest contributor explaining up to 67–77% of the total variance of these parameters. No sex or ethnicity difference in the variance components of BP circadian rhythm was observed.
Conclusion: This study suggests that ethnic differences in BP circadian rhythm already exist in youth with African Americans having a dampened circadian rhythm and better BP circadian rhythm may be achieved by changes in environmental factors.

Keywords: acrophase, African Americans, amplitude, blood pressure, circadian rhythm, twin study

Abbreviations: AIC, Akaike's information criterion; BP, blood pressure; CI, confidence interval; GEE, Generalized Estimating Equations; MAP, mean arterial pressure; SCN, suprachiasmatic nucleus

INTRODUCTION

As one of our biological rhythms, circadian rhythm, with a period of about 24 h, has been studied extensively and is demonstrated to be closely related to both the physiological and pathological functions of our cardiovascular organs. It is well known that the fluctuations of blood pressure (BP) show circadian rhythm, and higher night-time BP or loss of nocturnal dipping has been widely used to represent circadian variation in the past and has been linked with increased risk of target-organ damage and cardiovascular mortality [1–3]. This is particularly relevant to African Americans who start to display a higher night-time BP than European Americans from as early as age 10 years [4].

More recently, mathematic models using quantitative fitting to time-dependent BP recordings have offered new perspectives on the assessment of BP circadian rhythm [5–7]. Using this method, altered BP circadian rhythm has been described in many conditions causing increased cardiovascular risk, such as hypertension, chronic kidney disease, diabetes, obesity and small birth weight [8–13]. However, whether African Americans exhibit a different BP circadian rhythm from European Americans is unknown. Accordingly, the first aim of our study was to investigate whether there are ethnic differences in BP circadian rhythm in our Georgia Cardiovascular Twin study, which obtained 24 h ambulatory BP recording from a large sample of European American and African American youth and young adults.

METHODS

Participants

The present study constituted of participants from the Georgia Cardiovascular Twin Study, which was established in 1996 [14]. It included roughly equal numbers of African American and European American youth and young adults

Journal of Hypertension 2022, 40:163–170

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Received 4 May 2021 **Revised** 16 July 2021 **Accepted** 18 July 2021

J Hypertens 40:163–170 Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved.

DOI:10.1097/HJH.0000000000002988

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(>500 twin pairs), with the purpose to explore the change in relative influence of genetic and environmental factors on the development of cardiovascular risk factors. All twin pairs were reared together, and zygosity was determined using five standard microsatellite markers in DNA collected with buccal swabs. Participants were recruited from the Southeastern United States and were overtly healthy and free of any acute or chronic illness based on parental report. Study design, selection criteria and the criteria to classify participants as African Americans or European Americans basing on self-identification for this twin study have been described previously [15]. Participants' height and weight were measured with a Healthometer medical scale that was calibrated daily. BMI was calculated as weight/height^2 (kg/m^2).

A total of 760 individuals including 322 twin pairs (115 pairs of monozygotic twins, 196 pairs of dizygotic twins, and 11 pairs with unknown zygosity) and 116 singletons aged 12–30 years who had ABP measured from 2002 to 2006 during a routine scheduled examination and had qualified ABP recordings were included in this study. This study was approved by the Institutional Review Board of Augusta University, and performed following the guidelines of the Declaration of Helsinki. Written informed consent was obtained from participants at least 18 years. Both assent document from children and informed consent document from parents/guardians were obtained if participants were younger than 18 years.

Ambulatory blood pressure measurement

Participants underwent ambulatory BP monitoring for 24 h. Our procedures for these measurements have been described previously in detail [16]. Briefly, the cuff was fitted on the nondominant arm (model 90207; SpaceLabs, Redmond, Washington, USA). Measurements were obtained every 20 min during the daytime and every 30 min during the night. The daytime period was defined from 0800 until 2200 h. The night-time period was defined from 0000 to 0600 h. Acceptable readings were defined according to the following criteria: pulse pressure at least 20 mmHg and 140 mmHg or less; heart rate at least 40 and 180 beats/min or less. A qualified recording was defined as a minimal record length of 22 h and less than 3 h recording gap.

Parameters of blood pressure circadian rhythm

Reports have shown that the rhythm of BP can be well quantified using a multiple-component model consisting of cosine curves at different periods. An R package, Chronomics Analysis Toolkit (CATkit), was used to generate the BP circadian rhythm characteristics for this study [17]. Mean arterial pressure (MAP) rather than SBP or DBP was used because during oscillometer measurements, only MAP is measured and SBP or DBP are mathematically derived. Data were fitted with cosine curves by least squares regression. We mainly focused on parameters from the 24 h (circadian) period. The characteristics of MAP rhythm are listed in Fig. 1, including MESOR (Midline Estimating Statistic of Rhythm, a rhythm-adjusted mean), amplitude (difference between MESOR and highest value), and acrophase (time of the highest value of the curve with midnight as a fixed reference time). CATkit also provides the corresponding percentage rhythm. Percentage rhythm is obtained by least-square analysis and is equivalent to the R regression coefficient representing the fraction of the total variability that can be explained by the rhythm-fitted curve. A higher percentage rhythm value suggests that the rhythm-fitted curve variability is influenced mainly by a rhythm, not random variations, and thus, is commonly used as an indicator of rhythm integrity [8]. A circadian rhythm was detected if the cosine function fitted at the 24-h period has a significance with a P value less than 0.05. As the acrophase is a time point within a 24-h range (for example, there will be minimal difference between an acrophase of 23 : 59 and an acrophase of 00 : 10), therefore, to better describe the phase shift in a population study, we categorized the participants into two groups: in phase (with the time of the acrophase within 10th–90th percentile of the data) and out of phase (with the time of the acrophase >90th percentile or <10th percentile of the data). This concept was illustrated in Fig. 2.

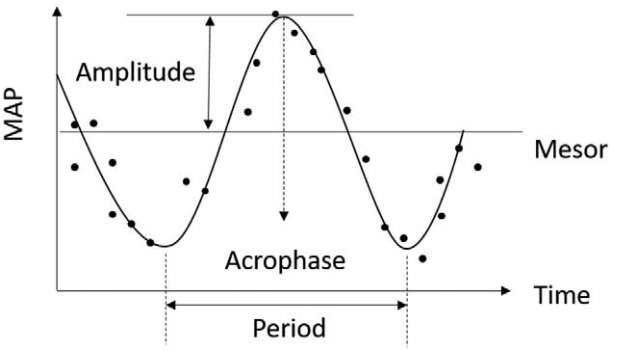

FIGURE 1 Definition of rhythm characteristics. Period = 24 h. MESOR is the value midway between the highest and lowest values of the fitted curve, amplitude (Amp) is the distance between MESOR and the highest value of the curve, and acrophase is the time of the peak of the fitted curve in relation to a fixed reference time (e.g. midnight).

Statistical analyses

The purpose of our analyses were: to test whether BP circadian parameters in African Americans were different from these in European Americans and to estimate the genetic and/or environmental sources of variance of BP circadian parameters and the extent to which they depend on ethnicity or sex.

Multiple regression: Generalized Estimating Equations (GEE) were used to test for effects of ethnicity, sex and their interaction on BP circadian parameters. GEE is a multiple regression technique that allows for nonindependence of twin or family data yielding unbiased standard errors and P values. Age and BMI were included as co-variates in the regression models. These analyses were conducted using STATA 16 (StataCorp, College Station, Texas, USA).

Quantitative genetic model fitting: structural equation modeling was used to answer the second aim of our study (Fig. 3). Details of model fitting of twin data have been described elsewhere [18]. In short, the technique is based on the comparison of the variance–covariance matrices in

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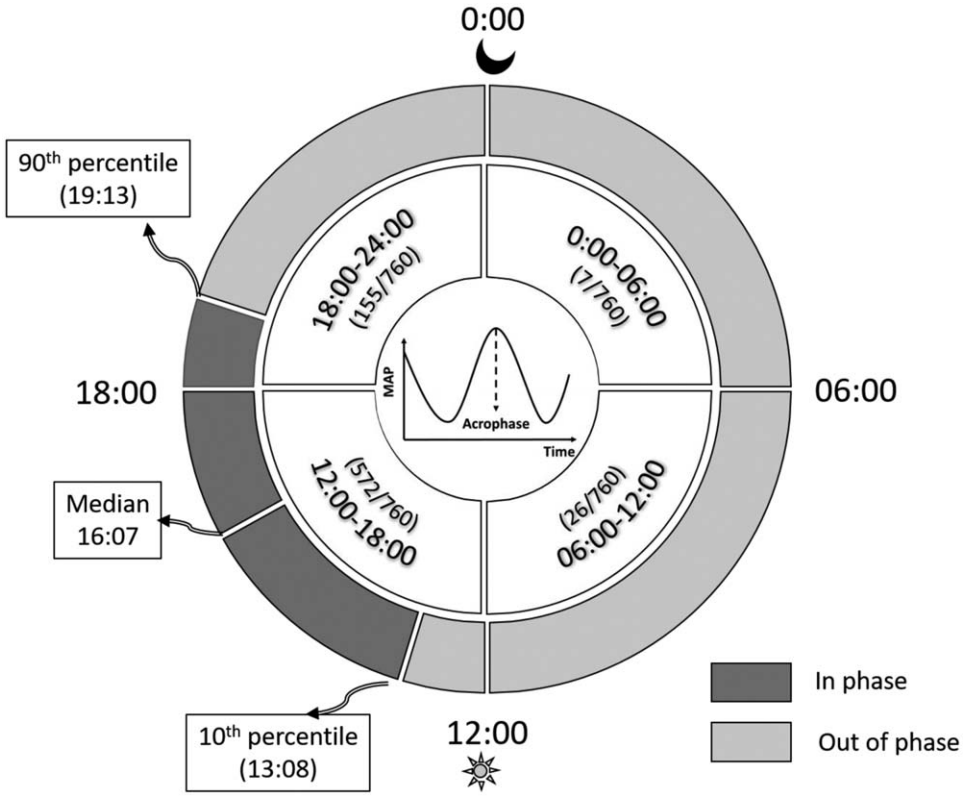

FIGURE 2 Definition of in phase/out of phase according to our data. In phase indicates that participants have their acrophase within 10th–90th percentile of the data. (Here it refers to the acrophase from 1308 to 1913 h); out of phase refers to participants with the phase greater than 90th percentile or less than 10th percentile of the data.

monozygotic and dizygotic twin pairs and allows separation of the observed phenotypic variance into its genetic and environmental components: additive (A) or dominant (D) genetic components and common (C) or unique (E) environmental components. Dividing each of these components by the total variance yields the corresponding standardized components of variance, for example, the heritability (h^2) can be defined as the proportion of the total variance explained by additive genetic variation. We focused on the additive genetic effects and common and unique environmental effects as there was little evidence that correlations among monozygotic twins substantially exceeded twice those among dizygotic twins, which indicates dominance variance. Genetic modeling was carried out with *Mx*, a computer program specifically designed for the analysis of twin and family data [19]. Models were fitted to the raw data using normal theory maximum likelihood allowing inclusion of incomplete data (i.e. when data were only available in one twin of a pair).

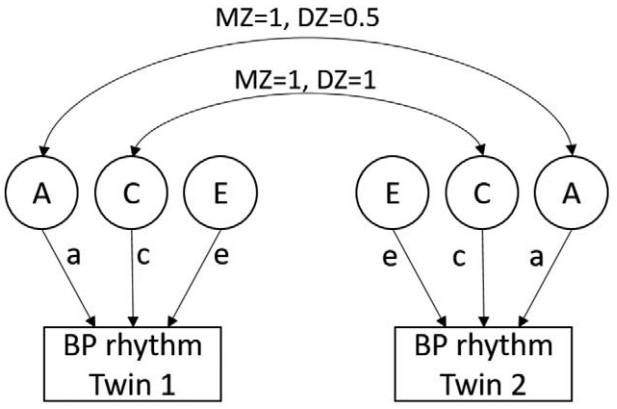

FIGURE 3 Path diagram for the structure equation modeling. Observed phenotypes for twin 1 and twin 2 are shown in squares, which refer to parameters, such as percentage rhythm, amplitude and in phase. Latent (i.e. unmeasured) factors are shown in circles. Correlations between additive genetic factors are 1 in monozygotic twins and 0.5 in dizygotic twins. The correlation is always 1 between common environmental factors for both monozygotic and dizygotic twins. Regression coefficients of observed variables on the different latent factors are shown in lower case: a = additive genetic effect, c = shared environmental effect, e = unique environmental effect.

Liability-threshold model

The heritability of the categorical variable of acrophase (i.e. in phase vs. out of phase) was assessed using a liability-threshold model. This model assumes a latent, normally distributed liability underlying the categorical phenotype [20]. In the current study, the underlying distribution was modeled to have one threshold, which allows for two categories, in phase and out of phase. Similar to a quantitative trait, sources of variation in this categorical variable considered in the modeling were additive (A) genetic, common (C) and unique (E) environmental factors.

Sex differences

Sex differences were examined by comparing a full model in which parameter estimates are allowed to differ in magnitude between men and women, with a reduced model in which parameter estimates are constrained to be equal across the genders. In addition to those models,

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TABLE 1. General characteristics by ethnicity and sex

	EA		AA		Ethnicity	Sex
	Males	Females	Males	Females	*P*	*P*
N	180	229	145	206		
Age (years)	16.6 ± 3.5	17.5 ± 3.4	16.7 ± 3.0	17.7 ± 3.4	NS	NS
Height[a] (cm)	170.1 ± 11.8	160.9 ± 10.1	171.3 ± 13.7	162.7 ± 6.3	<0.05	<0.001
BMI[a] (kg/m^2)	22.9 ± 5.7	22.6 ± 4.5	23.3 ± 5.8	25.7 ± 7.4	<0.001	<0.01
24 h MAP[b] (mmHg)	83.6 ± 5.8	81.5 ± 5.0	85.4 ± 6.1	83.9 ± 6.9	<0.001	<0.001
Daytime MAP[b] (mmHg)	87.6 ± 6.4	85.4 ± 5.6	88.2 ± 6.4	87.2 ± 7.7	<0.05	<0.001
Night-time MAP[b] (mmHg)	75.5 ± 7.2	73.7 ± 6.1	79.7 ± 7.8	77.2 ± 7.2	<0.001	<0.001

AA, African American; EA, European American; MAP, mean arterial pressure. Data are present as mean ± SD.
[a]Age was adjusted in the analysis.
[b]Age and BMI were adjusted in the analysis.

a scalar model was tested. In a scalar model, heritabilities are constrained to be equal across genders, but total variances may be different. All (nonstandardized) variance components for female participants are constrained to be equal to a scalar multiple, k^2, of the male variance components, such that $h_f^2 = k^2 h_m^2$, $c_f^2 = k^2 c_m^2$, $e_f^2 = k^2 e_m^2$ and $d_f^2 = k^2 d_m^2$. As a result, the standardized variance components, such as heritabilities are equal across sex, even though the unstandardized components differ.

Ethnicity differences

Ethnicity differences were examined by comparing a full model in which parameter estimates are allowed to differ in magnitude between African Americans and European Americans, with a reduced model in which parameter estimates are constrained to be equal across them. In addition to these models, a scalar model was tested in a similar fashion as done for sex.

Model-fitting procedure

Prior to analysis, effects of age were regressed out for all variables before using the residuals in model fitting. The significance of variance components A, C and E was assessed by testing the deterioration in model fit after each component was dropped from the full model. Standard hierarchic χ^2 tests were used to select the best fitting models in combination with Akaike's information criterion (AIC). The model with the lowest AIC reflects the best balance of goodness-of-fit and parsimony.

RESULTS

General characteristics and ethnicity difference in blood pressure circadian rhythm parameters

Descriptive statistics of the participants are presented by ethnicity and sex in Table 1. Male participants were taller than female participants, and African Americans had higher BMI than European Americans. African Americans and male participants also had higher 24 h MAP, daytime MAP and night-time MAP in comparison with European Americans and female participants after adjustment for age and BMI, which was consistent with our previous findings.

Among the 760 participants, 91.3% displayed a circadian rhythm in BP. By definition, 80% of participants' BP circadian rhythm were in phase, which corresponded to a range of acrophases from 1308 to 1913 h (Fig. 2). Table 2 displays the relationships among the different parameters of BP circadian rhythm. It clearly showed that percentage rhythm and amplitude were strongly related to the existence of circadian rhythm with the detection of circadian rhythm associated with higher percentage rhythm ($P = 8.11e{-}44$) and higher amplitude ($P = 7.24e{-}48$). Participants displaying circadian rhythm were also more likely to have BP rhythm in phase ($P = 0.027$). Similarly, participants with BP rhythm in phase had significantly higher percentage rhythm ($P = 0.007$) and were more likely to display circadian rhythm than participants with BP rhythm out of phase ($P = 0.025$).

As shown in Table 3, after adjusting for age and BMI, BP circadian rhythm showed a clear difference by ethnic group with African Americans having a lower percentage rhythm ($P = 2.8e{-}11$), a lower amplitude ($P = 1.5e{-}08$), a higher MESOR ($P = 2.5e{-}05$) and being more likely not to display circadian rhythm ($P = 0.002$) or not in phase ($P = 0.003$). There was also a sex difference in BP circadian rhythm with female participants having a lower MESOR ($P = 9.5e{-}06$), a lower amplitude ($P = 0.023$) and being more likely in phase ($P = 0.02$). We also observed that both percentage rhythm ($P = 0.002$) and amplitude ($P < 0.001$) were positively associated with age.

Quantitative genetic model fitting results

As there was a strong correlation between MESOR and 24-h BP ($r = 0.996$) and previous studies including ours have

TABLE 2. Blood pressure rhythm parameters in participants

	With rhythm	Without rhythm	*P* value	In phase	Out of phase	*P* value
N (%)	694 (91.3)	66 (8.7)		608 (80)	152 (20)	
Percentage rhythm (%)	33.7 ± 14.8	5.5 ± 3.6	8.11e-44	32.4 ± 15.8	26.9 ± 17.3	0.007
Amplitude (mmHg)	8.7 ± 3.0	2.8 ± 1.2	7.24e-48	8.3 ± 3.2	7.6 ± 3.8	0.088
In phase (%)	81.27	66.67	0.025	–	–	–
With rhythm (%)	–	–	–	92.76	85.53	0.027

Age, sex and ethnicity were adjusted in the analysis. Data are present as mean ± SD.

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TABLE 3. Blood pressure rhythm results by ethnicity and sex

	EA		AA		Ethnicity	Sex
	Males	Females	Males	Females	*P*	*P*
MESOR	83.4 ± 5.8	81.3 ± 5.0	85.3 ± 6.0	83.7 ± 6.9	2.5e−05	9.5e−06
Percentage rhythm (%)	35.5 ± 15.6	35.4 ± 16.4	25.6 ± 14.6	27.3 ± 15.6	2.8e−11	NS
Amplitude (mmHg)	9.2 ± 3.3	8.5 ± 3.2	7.5 ± 3.2	7.4 ± 3.1	1.5e−08	0.023
Participants with rhythm (%)	94.44	95.20	87.59	86.89	0.002	NS
Participants in phase (%)	82.78	86.90	68.28	78.16	0.003	0.02

Age and BMI were adjusted in the analysis. Data are mean ± SD. AA, African American; EA, European American; DZ, dizygotic twins; MZ, monozygotic twins.

found that the AE model has generally been the best fitting model for 24-h BP, we did not include MESOR in the current genetic modelling analysis. Furthermore, percentage rhythm and amplitude were used in the genetic modelling analysis to represent the existence of BP circadian rhythm rather than the categorical variables because of the fact that continuous variables have more power than categorical variable, and percentage rhythm and amplitude were strongly related with the detection of rhythm (by definition, the *P* value for the detection of rhythm indicates whether the amplitude is different from zero).

Intra-twin pair correlations for percentage rhythm and amplitude as well as the concordance rate for not in phase were listed in Table 4. In all ethnic groups, twin correlations or the concordance rate in monozygotic twin pairs are larger than those in dizygotic twin pairs, indicating genetic influences. We present the correlations collapsed over sex groups, as models that best explained the variance and covariance of these variables did not show any sex difference (see below).

Table 5 shows the model fitting results. For all the BP circadian rhythm parameters, the model fitting suggested that there were no significant ethnicity or sex differences in variance component estimates. Also for all the BP circadian rhythm parameters, the best fitting model was the ACE model, which means the variance of BP circadian rhythm depends on additive genetic factors (A), common environmental factors (C) as well as unique environmental factors

TABLE 4. Intra-twin pair correlations by zygosity in European American and African American

	EA		AA		EA and AA combined	
Measure	MZ	DZ	MZ	DZ	MZ	DZ
n (pairs)	71	96	44	100	115	196
Percentage rhythm	0.29	0.18	0.19	0.15	0.25	0.16
Amplitude	0.29	0.23	0.20	0.15	0.25	0.19
Phase[a]	0.38	0.21	0.63	0.41	0.53	0.34

[a]Indicates pairwise concordance rate for not in phase. AA, African American; EA, European American; DZ, dizygotic twins; MZ, monozygotic twins.

TABLE 5. Model fitting results

Percentage rhythm					
Models	**−2LL**	**AIC**	**$\Delta\chi^2$**	**Δdf**	***P***
ACE	6080.65	4624.65			
AE	6081.03	4623.03	0.38	1	0.54
CE	6081.03	4623.03	0.38	1	0.54
E	6093.04	4633.04	12.39	2	0.002
Amplitude					
Models	**−2LL**	**AIC**	**$\Delta\chi^2$**	**Δdf**	***P***
ACE	3753.24	2297.24			
AE	3753.97	2295.97	0.73	1	0.39
CE	3753.48	2295.48	0.24	1	0.62
E	3767.58	2307.58	14.34	2	0.0008
In phase					
Models	**−2LL**	**AIC**	**$\Delta\chi^2$**	**Δdf**	***P***
ACE	683.59	−764.41			
AE	683.59	−763.98	0	1	1
CE	686.02	−766.41	2.43	1	0.12
E	700.15	−751.85	16.56	2	0.0003

$\Delta\chi^2$, difference in chi-square; Δdf, difference in degrees of freedom; −2LL, minus twice the log likelihood; AIC, Akaike information criteria; A, additive genetic; C, common environment; E, unique environment.

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TABLE 6. Parameter estimates and 95% confidence interval of best fitting models

Best model		Variance component estimates (95% confidence intervals)		
		a^2	c^2	e^2
Percentage rhythm	ACE	0.13 (0.00–0.39)	0.10 (0.00–0.30)	0.76 (0.61–0.91)
Amplitude	ACE	0.11 (0.00–0.41)	0.14 (0.00–0.32)	0.74 (0.59–0.89)
In phase	ACE	0.33 (0–0.46)	0.00 (0.00–0.28)	0.67 (0.54–0.85)

Mean values of all variables were adjusted for age, ethnicity, sex, and their interactions. A/a^2, additive genetic; C/c^2, common environment; E/e^2, unique environment.

(E). Although the model assuming the absence of the genetic component (CE vs. ACE model, $P = 0.54$, 0.62 and 0.12 for percentage rhythm, amplitude and phase, respectively) and the model assuming the absence of the common environmental factor fitted the data well (AE vs. ACE model, $P = 0.54$, 0.39 and 1 for percentage rhythm, amplitude and phase, respectively), the model assuming the absence of both components (E vs. ACE model, $P = 0.002$, 0.0008 and 0.0003 for percentage rhythm, amplitude and phase, respectively) was significantly worse. This indicates that BP circadian rhythm did show familial aggregation to some degree, either because of additive genetic and/or common environment influence but its variation in the population could not be explained by unique environment effects alone. For the phase variable, a significant scalar effect for ethnicity was found, indicating that European Americans show larger variability in phase than do African Americans.

Variance component parameters estimated from the best models are shown in Table 6 including 95% confidence intervals (95% CIs). The variances of BP circadian rhythm were predominantly because of unique environmental components (ranges from 67 to 76%). The additive genetic component had a small contribution to BP circadian rhythm (ranges from 11 to 33%), as did the shared environmental component (ranges from 0 to 14%). However, as the 95% CI of unique environmental component does not include one in all traits, the other part of the BP circadian rhythm variance must be genetic and/or common environmental components. These small influences of A and/or C combined did have a significant contribution to the total variance of BP circadian rhythm, accounting for 23, 25 and 33% of the total variance of percentage rhythm, amplitude and phase, respectively.

DISCUSSION

This study is the first to demonstrate the existence of ethnic differences in BP circadian rhythm. We observed that African American youth and young adults display significantly altered BP circadian rhythms compared with European Americans as indexed by a lower amplitude, a lower percentage rhythm, a higher possibility of not displaying circadian rhythm and a higher possibility of not being in phase. This is also the first study evaluating the relative impact of genetic and environmental influences on BP circadian rhythm. Despite the major contribution of unique environment factors to the variance of BP circadian rhythm, some familial aggregation (explaining about 23–33% of the variance) either because of additive genetic and/or common environment influences was identified.

Ethnic differences in day/night BP levels and patterns have been well documented with African Americans having a higher night-time BP and a blunted nocturnal decline in comparison with European Americans, and a higher risk for cardiovascular disease because of persistently higher BP load throughout the 24 h day [4,21,22]. In this study, we further extend the finding of ethnic difference to parameters of BP circadian rhythm obtained from Fourier analysis, an approach considering all the time points and giving better quantification of BP circadian rhythm. Similar to previous studies, we also observed a correlation between BP circadian rhythm parameters and night-time BP or BP dipping (Supplementary Table 1, http://links.lww.com/HJH/B759). However, the ethnic differences exist even after the adjustment of night-time BP or BP dipping (Supplementary Table 2, http://links.lww.com/HJH/B759), indicating that the ethnic differences in BP circadian rhythm is a feature independent of the ethnic difference in night-time BP or nocturnal decline. Studies [8–11,13,23] on BP circadian rhythm in other ethnic groups have demonstrated that there is an increasing perturbation of BP circadian rhythm, indexed by blunted rhythm amplitude and/or phase change, in participants with increased cardiovascular risk. In combination with the findings in experimental models that circadian desynchronization decreases survival rates [24–26], the altered BP circadian rhythm in African Americans may indicate an impaired adaptation to 24 h conditions, which could contribute to a persistent challenge to the homeostasis in addition to the persistent BP load at night.

It is noteworthy that our study is the first study to investigate the relative contribution of genetic and environmental factors to the variation of circadian BP rhythm in the general population. It is also the first twin study to include both African Americans and European Americans, and found that the relative contributions of genetic and environmental factors to circadian BP rhythm in African Americans were similar to those in European Americans, with genetic factors and common environmental factors together accounting for 23 to 33% of the total variance. Unique environmental factors were the largest contributor explaining up to 67–76% of the total variance. It is well known that BP is the measure of force that blood places on the walls of blood vessels and is regulated by a number of different systems, such as central and autonomic nervous system, the kidneys, the heart, the vasculature and the immune system. On the other hand, circadian mechanisms are known to play an important role in the regulation of BP oscillation [27,28]. The circadian clock genes are found in nearly all cells with the central circadian pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus, and

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peripheral oscillators varying in a tissue-specific manner. The molecular and genetic evidence linking the circadian clock genes to BP control was shown by Witte *et al.* [29], who established that SCN is crucial to the daily rhythmic variation of BP in rat in 1998, and Curtis *et al.* [30] who demonstrated that core clock genes, such as *BMAL1* and *CLOCK* are indispensable for the circadian rhythm in BP. In addition to the pacemaker in SCN, more evidence has emerged that peripheral clock mechanisms are involved in regulation of BP circadian rhythm. Yang *et al.* [31] found that BP oscillation was also abolished in tamoxifen induced conditional *Bmal1* knockout mice, and Xie *et al.* [32] found that the amplitude and acrophase in blood pressure circadian oscillation were significantly altered in mice lacking the smooth-muscle *Bmal1* gene, whereas the *Bmal1* gene in brain remains intact. Moreover, work from Zuber *et al.* [33] demonstrated that *clock* knockdown resulted in significant changes in renal expression of vasopressin V2 receptor and aquaporin, which regulate water balance, and loss of *clock* resulted in a mixed phenotype of partial diabetes insipidus, impaired sodium excretion and blood pressure regulation. Although the internal clock system determines the BP circadian rhythm, environmental and behavior factors, such as light intensity, smoking, emotional/mental stress, sodium intake, physical activity/exercise and sleep patterns in human beings, can significantly shift the BP circadian as well [34]. This is confirmed by our results with unique environmental factors explaining the majority of the variance. Controlling for these masking factors at the constant and minimal level (a constant routine protocol [35]) or by separation of the environmental effects from the internal clock (a forced desynchrony protocol [36]) are commonly used methods to study the circadian rhythm in human beings in experimental settings. Our findings suggest that gene finding efforts for BP circadian rhythm may need the same approach to control environmental confounding factors.

In this study, we focused on circadian BP parameters. Ultradian rhythms (i.e. those rhythmic components with a period <24 h) in BP are known to exist and determination of ultradian components of BP rhythm has often been used as a tool to improve accuracy of the mathematical analysis of 24-h rhythm parameters [6]. However, the cause of these rhythms is still unclear with some ultradian rhythm being attributed to periodic daily activities, such as food intake [13]. Furthermore, the parameters of the overall rhythm are most strongly influenced by the circadian rhythm in children [6], which was also the case in the current study (Supplementary Table 3, http://links.lww.com/HJH/B759). In this study, we also categorized acrophase by defining the two extreme ends of the distribution (<10% or >90%) as out of phase. This definition is based on the fact that acrophase calculated from one single ABP measurement directly refers to a time point that ranges from 0 to 24 and the two extreme ends (0 : 00 and 24 : 00) of this circular data actually has no difference from a biological point of view.

We need to be cautious in the interpretation of our findings. First, as the Georgia Cardiovascular Twin Study is constituted of youth and young adults, the generalizability of these results to other adult populations remains to be determined. Second, our overall sample size was substantial for twin ABP studies but might not have enough power to detect small ethnic or sex difference in the heritability of the BP circadian rhythm. Further twin studies with large sample sizes involving multiethnic groups are warranted. Third, the quantification of BP rhythm analysis was based on a single ABP measurement. Continued follow-up of this twin cohort including ABP measurements with multiple days at multiple time points will provide more solid evidence on the genetic and environmental sources of BP circadian rhythm. In addition, endogenous circadian markers, such as core body temperature, dim light melatonin onset and rest–activity rhythm, should also be measured for better definition of phase changes. Furthermore, several factors have been hypothesized to account for the well established ethnic differences in night-time BP/nocturnal dipping, such as obesity, sleep duration and sodium intake. In the current study, we were able to test the effect of obesity (indexed by BMI); however, the lack of measurements on sleep and sodium intake as well as better measurements of adiposity in the previous visits of the GA twin cohort prevents us from further exploring these effects in the current study.

In conclusion, we have demonstrated a blunted BP circadian rhythm in African Americans in youth and young adults, independent from previous findings on the higher night-time BP or blunted dipping. The impaired adaptation to 24 h conditions in African Americans may be one of the reasons for the disproportionately high incidence of hypertension and associated mortality in this ethnic population. Although the variation of BP circadian rhythm in the population does show some familial aggregation, the major contributors are unique environmental factors, suggesting that better BP circadian rhythm can be achieved by changes in environmental factors, such as lifestyle and behaviors.

ACKNOWLEDGEMENTS

The Georgia Cardiovascular Twin study is currently supported by grants DK117365 and MD013307 from the National Institute of Health.

The authors had full access to the data and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written. All authors have stated that there were no financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest.

Conflicts of interest

There are no conflicts of interest.

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